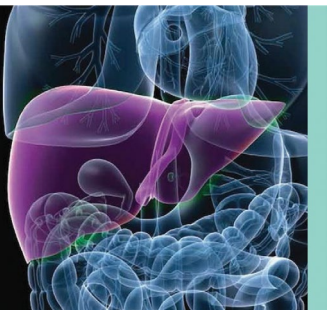

Hepatopulmonary Syndrome and Portopulmonary Hypertension: The Pulmonary Vascular Enigmas of Liver Disease

Michael J. Krowka, M.D.

With the advent of successful liver transplantation came a renewed interest in what we now appreciate as two distinct adverse pulmonary vascular consequences of advanced liver disease: hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). The interest was not simply academic. Indeed, once these entities were recognized and accurately characterized, it was clear that their natural histories and effects on both attempts at and outcomes of liver transplantation could be quite concerning.

Given millennia of experience with cirrhosis, had these pulmonary complications always been around and were they simply not recognized as such because of the absence of characterization of the syndromes, lack of diagnostic criteria, and/or failure to appreciate their clinical importance? Perhaps. And so, as a prelude to a historical review of these entities, and to help clarify the frequent confusion between the two syndromes, a concise, comparative summary of characteristics of each syndrome is provided in Table 1.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ECMO, ECMO, extracorporeal membrane oxygenation; ERA, endothelin receptor antagonist; ERS, European Respiratory Society; HPS, hepatopulmonary syndrome; ILTS, International Liver Transplant Society; IPVD, intrapulmonary vascular dilatation; IV, intravenous; LD, liver disorder; L-NAME, N^G-nitro-L-arginine methyl ester; LT, liver transplant; MELD, Model for End-Stage Liver Disease; MIGET, multiple inert gas elimination technique; mPAP, mean pulmonary artery pressure; NIH, National Institutes of Health; PaO_2, partial pressure of arterial oxygen; PBC, primary biliary cirrhosis; PH, pulmonary hypertension; POPH, portopulmonary hypertension; PV, pulmonary vasoactive; PVR, pulmonary vascular resistance; REVEAL, Registry to EValuate Early And Long-term pulmonary artery hypertension disease management; ^{99m}TcMAA, technetium macroaggregated albumin; UNOS, United Network for Organ Sharing; WHO, World Health Organization.

TABLE 1. DISTINCTIONS BETWEEN HPS AND POPH

Characteristics	HPS	POPH
Clinical issue*	Arterial hypoxemia caused by IPVD	Pulmonary artery hypertension
Diagnostic criteria†	PaO_2 < 80 mm Hg	mPAP > 25 mm Hg; PVR > 3 wood units
LD	Usually cirrhosis	Always portal hypertension
Severity	Poor correlation with LD	Poor correlation with LD
Frequency seen	5%-32%	5%-10%
Medical treatments‡	Wear supplemental oxygen	PV medications
5-Year survival rate	23% (no treatments)	4%-14%; 40% survival rate with PV therapy only
LT§	An "indication"	A "contraindication" if mPAP > 45 mm Hg
Treatment outcomes‖	Complete resolution with LT	Unpredictable, 50% resolution with LT

*IPVDs were determined by contrast-enhanced transthoracic echocardiography.
†PaO_2 determined by arterial blood gas in the sitting position breathing room air; right heart catheterization measures/calculates mPAP and PVR, respectively.
‡Several available for POPH, but only one randomized, placebo-controlled trial conducted; no controlled trials in HPS to date.
§Increased LT risk. Expedited LT consideration if pretransplant PaO_2 < 60 mm Hg (HPS); if mPAP < 35 mm Hg with PV therapy (POPH).
‖Time resolution of HPS related to severity of hypoxemia; PV therapy in POPH can be discontinued in 50% after LT.

EARLY HISTORY

Hepatopulmonary Syndrome

Why does arterial blood lack oxygen in the setting of liver disease? That simple question was first addressed in 1894 by Dr. M. Fluckiger[1] with the support of Professor F. D. von Recklinghausen, who conducted the autopsy on his 37-year-old patient who died of massive hematemesis and cirrhosis of the liver caused by syphilis. Subsequently, complex explanations for arterial hypoxemia over the years have culminated in the description of an entity, coined by Kennedy and Knutson[2] in 1977 as the "hepatopulmonary syndrome." It was not until 1998 that a seminal review article regarding the pulmonary vascular disorders in portal hypertension was published by French investigators.[3] This article described potential pathophysiological mechanisms based on clinical experiences; it paved the way for the first animal model for HPS described by Chang[4] from Northwestern University and subsequently expanded on and continued in-depth by Fallon and colleagues[5] at the University of Alabama.

Portopulmonary Hypertension

The observation that pulmonary hypertension (PH) could complicate portal hypertension was first made by Mantz and Craig[6] at the University of Minnesota in 1951. The link between PH and portal hypertension was initially thought to be caused by pulmonary emboli originating from the portal venous territory and passing through portosystemic shunts to reach the pulmonary circulation. In addition to emboli, subsequent autopsy studies have demonstrated other pathologies.[7] Specifically, thrombosis in the pulmonary arteries could be caused by constriction of its peripheral, that is, muscular arterial branches, by endothelial/smooth muscle proliferation, intimal lesions including proliferation and fibrosis, dilatation lesions and platelet aggregates, but not an embolic phenomenon. The constellation of these nonembolic changes was termed "plexogenic arteriopathy," which derives from the Latin word *plexus* meaning a "braid." The network/web morphology metaphor is borrowed from neuroanatomy—remember nerve plexuses. The term "plexiform" has been used to indicate the stage of the lesion, but it is best given a wide berth to avoid confusion.[8] The unifying idea was an obstruction to pulmonary arterial flow caused by mediators emanating from or bypassing the portal circulation. The entity was termed "portopulmonary hypertension," a phrase arguably first used by Yoshida et al.[9] in 1993. Despite the clinical and hemodynamic characterizations of PH in the setting of

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liver disease, no experimental animal model exists to date for POPH.

THE FIRST "LIVER-LUNG" CONFERENCE

In 1990, a small group of clinicians convened at the Mayo Clinic satellite practice in Jacksonville, Florida, for what was arguably the first international gathering to discuss "liver-lung" problems (Fig. 1). This was the first national or international conference that I could find that included a talk on the topic of HPS; a fitting (and appreciative) lecturer for the inaugural presentation was Dame Sheila Sherlock (1918-2001)[10] of the Royal Free Hospital in London (Fig. 2). Interestingly, the topic of pulmonary artery hypertension as a complication of liver disease was given scant attention, but subsequent anecdotes of liver transplant (LT) failures in the setting of that disorder would soon become apparent in the late 1990s.

As a final aside, the liver-lung theme also included a lecture on sarcoidosis, provided by the husband of Prof. Sherlock, David Geraint (Gerry) James (1922-2010), M.D., F.R.C.P.

COMMITTEE AT WORK

During the 2000 European Respiratory Society (ERS) Annual Congress held in Florence, Italy, experts in pulmonology and hepatology held a symposium entitled "Advances in Understanding Pulmonary Complications in Hepatic Diseases." From this symposium was born the ERS Task Force on Pulmonary-Hepatic Disorders that subsequently published its landmark paper in 2004[49] (Fig. 3) that had three goals: (1) to increase awareness of HPS and POPH; (2) to improve diagnosis and management; and (3) to suggest and stimulate research. The diagnostic criteria and suggestions put forth by that Task Force remain the guideposts followed today.

TRANSPLANT DISAPPOINTMENTS AND SUCCESSES

There has been a remarkable evolution of experience and expectations when confronted with these pulmonary vascular syndromes in LT candidates. No proven medical therapies for HPS have evolved via controlled trials, the most recent being a National Institutes of Health (NIH)–sponsored, multicenter, prospective, randomized, placebo-controlled trial using sorafenib to attenuate angiogeneis[11] (although supplemental oxygen can improve hypoxemia). POPH can be improved, but not be cured, with pulmonary artery vasomodulators alone. Hence with poor outcomes of the "natural histories" of both syndromes, attempts and experiences to resolve them with liver transplantation have evolved.

Notably, only one randomized, placebo-controlled trial has been accomplished in patients with POPH, PORTICO.[12] This trial recently reported a significant reduction in pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP; compared with controls) using the endothelin receptor antagonist (ERA) macitentan over a 12-week period. Implications of these findings for liver transplantation will be of interest.

Hepatopulmonary Syndrome

In a 1968 report, Starzl et al.,[13] while at the University of Colorado, described the extended survival after orthotopic homotransplantation of three children who "had evidence of the venous-to-arterial intrapulmonary shunts." Interestingly, the oxygen saturations were 85% to 88% breathing room air and did not improve breathing pure oxygen. The shunts were calculated to be approximately 50% of the cardiac output and did improve significantly over a 10-day period posttransplant. However, in 1984, Van Thiel et al.[14] from the University of Pittsburgh proposed, but without providing specific data, that a partial pressure of arterial oxygen (PaO_2) <50 mm Hg due to pulmonary shunts should be an "absolute contraindication" to liver transplantation. These authors had noted "empirically that shunts that do not close postoperatively for periods of up to several weeks and that the resultant hypoxemia experience post-operatively, is yet another adverse factor that frequently turns a hopeful situation into a hopeless effort."

By the early 1990s, a series of case reports demonstrated that varying degrees of HPS *could* resolve after LT in adults and children. Over time, with mounting successes combined with a dismal outlook if transplant was not done (5-year survival rate of 23%), HPS became an "indication" for LT.[15] Importantly, because of the poor correlation between the severity of HPS and the severity of liver disease, current American Association for the Study of Liver Diseases (AASLD) guidelines from the AASLD and the International Liver Transplant Society (ILTS) suggest holding an "expedited review"

Symposium: The Liver-Lung Interface

January 12, 1990 7:30 a.m. to 5:30 p.m.

Symposium: The Liver-Lung Interface is an update on state-of-the-art understanding of clinical and pathophysiological aspects of the liver-lung relationship.

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Program Lectures and Discussions

JANUARY 11
Evening Registration 6:30 - 7:30 p.m.

JANUARY 12

7:30 a.m.	**REGISTRATION** Continental Breakfast
8:10	**WELCOME:** *Michael J. Krowka, M.D.* Mayo Clinic Jacksonville
8:15	**ALPHA$_1$ ANTITRYPSIN DEFICIENCY:** A Liver Disorder with Lung Manifestations *Ronald G. Crystal, M.D.* National Institutes of Health, Bethesda, Maryland
8:45	**HEPATO-PULMONARY SYNDROME** *Dame Sheila Sherlock, M.D., F.R.C.P.* Royal Free Hospital, London
9:15	**PULMONARY VASCULAR PATHOLOGY IN LIVER DISEASE** *Lynne M. Reid, M.D.* Harvard University
9:45	**NEUROPEPTIDES: A LIVER-LUNG RELATIONSHIP?** *Thomas M. O'Dorisio, M.D.* Ohio State University
10:15	Discussion
10:30	Coffee
11:00	**LIVER-LUNG GRANULOMAS** *D. Geraint James, M.D., F.R.C.P.* University of London
11:30	**PRIMARY BILIARY CIRRHOSIS AND THE LUNG** *E. Rolland Dickson, M.D.* Mayo Clinic Rochester
12:00 p.m.	Discussion
12:30	Lunch
2:00	**PULMONARY GAS EXCHANGE IN LIVER DISEASE** *Denis A. Cortese, M.D.* Mayo Clinic Rochester; *Robert Rodriquez-Roisin, M.D.* University of Barcelona, Spain
3:00	Discussion
3:15	Coffee
3:30	**LIVER TRANSPLANTATION: PERIOPERATIVE ICU EXPERIENCE** *David J. Plevak, M.D.* Mayo Clinic Rochester
4:00	**EFFECT OF LIVER TRANSPLANTATION ON LUNG FUNCTION** *Michael J. Krowka, M.D.* Mayo Clinic Jacksonville
4:30	Discussion
4:45	**OVERALL REVIEW:** *Dame Sheila Sherlock*
5:30	Cocktail Hour

For further information call (904) 223-2058

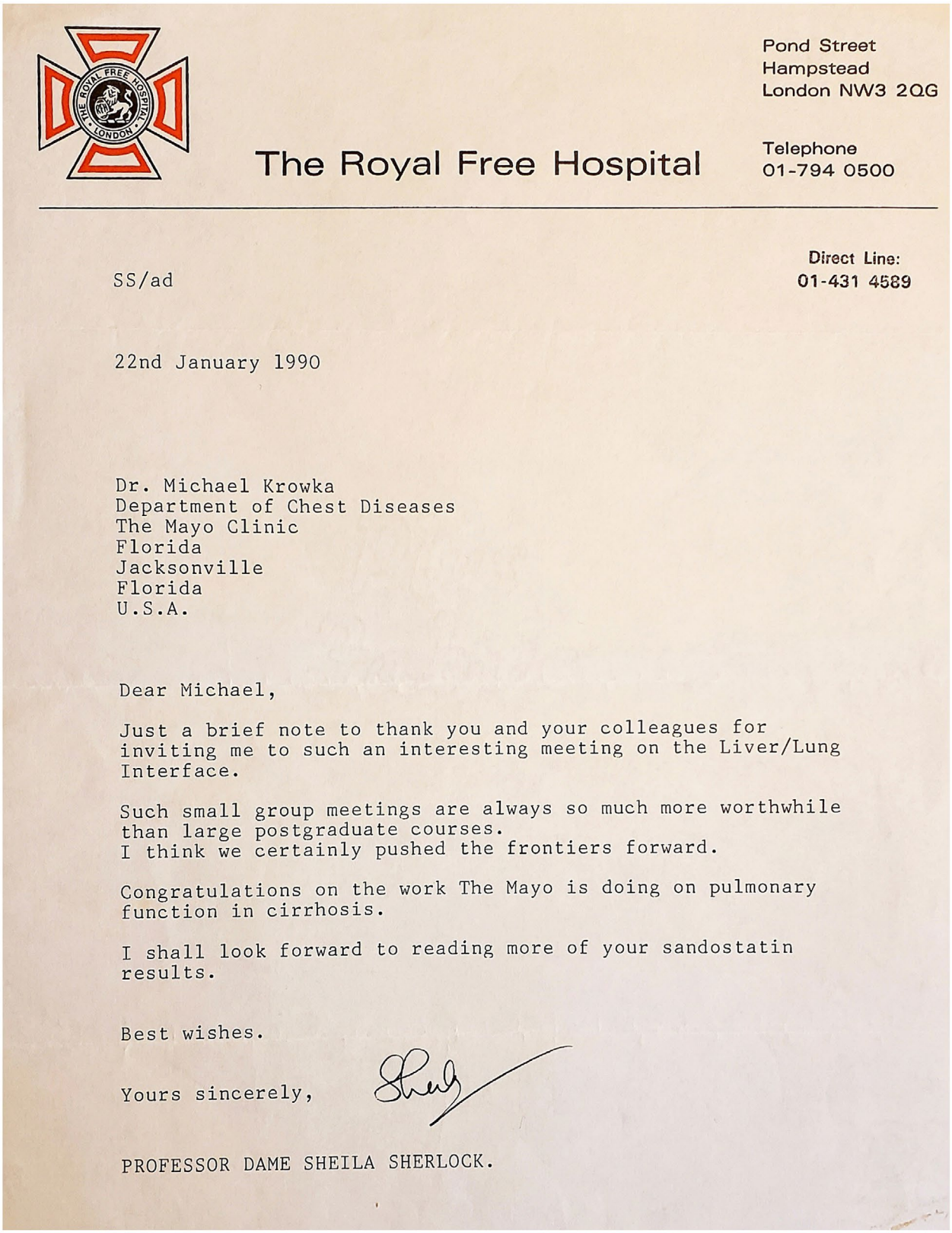
Registration Information and Accommodations

Please complete the attached registration form and mail it with the $150.00 fee to Mayo Clinic Jacksonville, Postgraduate Courses, 4500 San Pablo Road, Jacksonville, Florida 32224 by December 12, 1989. Your registration fee will be refunded if cancellation is made by January 5, 1990.

The course will be held in the Conference Center at the Marriott at Sawgrass. A block of rooms at a special rate of $90.00, plus tax and gratuity, has been reserved at Marriott at Sawgrass Resort for this conference. This rate applies only for reservations made before December 25, 1989. Call 1-800-872-7248 or 904-285-7777 and identify your affiliation with this course. Additional hotel and motel accommodations are available only five to ten minutes away by car. For further information call Mayo Clinic Jacksonville, (904) 223-2058.

FIG 1 The first liver-lung conference that had HPS as a unique meeting topic. The conference was held at the Mayo Clinic, Jacksonville, Florida, campus and featured renowned physicians who spoke to an audience of approximately 30 people.

for transplant consideration. To that end, in the setting of HPS, a "Model for End-Stage Liver Disease (MELD) score exception" policy currently exists for moderate to severe HPS (PaO_2 < 60 mm Hg).[16] It remains prudent to advise that the transplant be done in experienced centers, especially when the arterial hypoxemia is severe



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22nd January 1990

Dr. Michael Krowka
Department of Chest Diseases
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Dear Michael,

Just a brief note to thank you and your colleagues for inviting me to such an interesting meeting on the Liver/Lung Interface.

Such small group meetings are always so much more worthwhile than large postgraduate courses.
I think we certainly pushed the frontiers forward.

Congratulations on the work The Mayo is doing on pulmonary function in cirrhosis.

I shall look forward to reading more of your sandostatin results.

Best wishes.

Yours sincerely,

PROFESSOR DAME SHEILA SHERLOCK.

FIG 2 A thank-you letter from Dame Sheila Sherlock after the liver-lung conference at Mayo Jacksonville. The subsequent "proof-of-concept" use of Sandostatin, referred to in her letter to treat HPS, was a failure.

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ERS TASK FORCE

Pulmonary–Hepatic vascular Disorders (PHD)

R. Rodríguez-Roisin*, M.J. Krowka#, Ph. Hervé¶, M.B. Fallon+, on behalf of the ERS Task Force Pulmonary–Hepatic Vascular Disorders (PHD) Scientific Committee

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FIG 3 ERS Task Force Recommendations for the Screening, Diagnosis and Management of Pulmonary-Hepatic Vascular Disorders. Two international consensus conferences were held to characterize and develop diagnostic criteria for the pulmonary vascular syndromes in liver disease. The final Consensus Conference, held in Barcelona, Spain, chaired by Dr. Rodriguez-Roisin from Barcelona and Dr. Krowka from Rochester, Minnesota. The diagnostic criteria agreed on and published from that gathering are still followed as of this writing, as exemplified by this report from the ERS Task Force.

(PaO_2 < 50 mm Hg), because of the challenges in the immediate posttransplant critical care time period.[17] Despite the severity of HPS, expecting complete resolution of the syndrome posttransplant in the era of MELD exceptions has become the norm.[18]

Portopulmonary Hypertension

Outcomes after LT attempts in the setting of POPH and the reporting of those outcomes, have followed a rather tumultuous course since the first descriptions in the early 1990s. Yoshida et al.,[9] from the University of Western Ontario, described two interesting cases of POPH: one (extrahepatic portal hypertension) treated with a single lung transplant and one (chronic active hepatitis) treated with a LT. Pulmonary artery hypertension recurred in the transplanted lung 5 months posttransplant but was cured in the other patient with a successful LT. This was the first suggestion that the liver was the culprit inducing pulmonary artery hypertension. Over the years, private discussions at national meetings alluded to the unexpected occurrences of intraoperative death when transplant was attempted in the setting of POPH, as first reported in the literature by Ramsay et al.,[19] at Baylor Medical Center, Dallas, Texas. Subsequent descriptions of transplant attempts and outcomes in the setting of POPH were summarized in a literature review and substantiated in a multicenter database experience.[20,21] In analyzing POPH transplant outcomes in 75 patients, a pretransplant mPAP >35 mm Hg appeared to be associated with poor survival during the transplant hospitalization (35% mortality rate). Variable use of intravenous

TABLE 2. HPS: A CHRONOLOGY OF SELECTED MILESTONES

Year	First Author	Observation/Contribution
1884	Fluckiger[1]	Cyanosis, clubbing in cirrhosis first described
1938	Keys[30]	Hypoxemia in cirrhosis caused by rightward shift of the hemoglobin/oxygen (Hgb-O_2) curve
1953	Wilson[31]	Hypoxemia in cirrhosis due to "venous admixture" rather than Hgb-O_2 curve shift
1956	Rydel[32]	First clinic pathological case report of HPS
1957	Calabresi[33]	Unusual portal to pulmonary vein connections described
1960	Rodman[34]	"Unsaturation of arterial blood" due to venous admixture common in cirrhosis
1963	Mellemgaard[35]	Portal to pulmonary vein connections *unlikely* to contribute to hypoxemia
1966	Berthelot[36]	Lung pathologies of vascular dilatation and possible angiogenesis described
1968	Starzl[13]	First LTs attempted in the setting of presumed intrapulmonary shunting
1977	Kennedy[2]	The term "hepatopulmonary syndrome" first coined
1984	Van Thiel[14]	HPS with PaO_2 < 50 mm Hg an "absolute contraindication" to LT
1987	Krowka[37]	Small series using almitrine bismesylate for HPS; no improvement in PaO_2
1988	Maddrey[38]	HPS with PaO_2 < 50 mm Hg a "relative contraindication" to LT
1989	Edell[39]	MIGET characterized reasons for the hypoxemia of HPS
1990	Krowka[40]	Screening for HPS using contrast-enhanced transthoracic echocardiography described
1990	Stoller[41]	HPS resolves in an adult with PBC after LT
1992	LaBerge[42]	HPS resolves in two children after LT
1992	Chang[4]	Common bile duct ligation experimental model in a rat developed for HPS
1996	Krowka[15]	Mayo cases and literature review: progressive HPS an "indication" for HPS
1997	Fallon[5]	First describes nitric oxide implication in the rat model of HPS
1998	Whyte[43]	Use of ^{99m}TcMAA lung-brain scanning quantifies HPS severity
1999	Martinez[44]	Association between HPS and other common respiratory disorders described
1999	Egawa[45]	Living donor LT for HPS reported and excellent long-term outcomes
2000	Schenk[46]	Small series showing IV methylene blue improved HPS hypoxemia in intensive care unit setting
2003	Taille[47]	Resolution of HPS post-LT dependent on severity pretransplant
2003	Schenk[48]	HPS reported as an independent risk for poor outcome in liver disease
2004	Rodriguez-Roisin[49]	ERS consensus committee defines HPS diagnostic criteria
2005	Swanson[50]	5-Year natural history (without transplant) of HPS described
2006	Fallon[16]	MELD exception criteria (PaO_2 < 60 mm Hg) for HPS began
2006	Gomez[51]	Nebulized L-NAME decreased exhaled nitric oxide but does not improve PaO_2 in HPS
2008	Rodriguez-Roisin[52]	*New England Journal of Medicine* review article: hepatopulmonary syndrome: liver-induced lung vascular disorder
2008	Fleming[53]	Use of ECMO after LT for refractory HPS
2010	Roberts[54]	Genetic risk factors for HPS described
2010	Gupta[17]	Excellent LT outcome in severe HPS (PaO_2 < 50 mm Hg)
2013	Iyer[18]	Excellent LT outcomes for HPS in the era of MELD exception
2014	Goldberg[55]	Impact of MELD exception for HPS described from the UNOS database
2016	Krowka[26]	ILTS consensus practice guidelines for HPS published
2019	Raevens[56]	Excellent HPS outcomes after LT: Eurotransplant experience
2019	Kawut[11]	First randomized, controlled trial in HPS (sorafenib); no improvement in PaO_2

(IV) prostacyclin to treat POPH was a very limited, yet a hopeful and an anecdotal approach to improve POPH posttransplant survival.

POPH 5-year survival rates without medical treatment and with uncontrolled medical treatments, but not LT, have ranged from 14% to 40%, respectively.[22,23] There has never been a controlled trial to assess pulmonary vasodilator therapy impact in liver transplantation. Intuitively, it seemed reasonable to treat transplant patients with POPH *before* they experienced development of moderate-to-severe POPH *and* to attempt transplant if treatments could improve the hemodynamic and right ventricular function. To that end, and because of the poor correlation between the severity of POPH and the severity of liver diseases, a MELD exception for POPH was proposed and initiated in 2006.[24]

This approach has been justified because approximately 50% of patients with POPH, treated successfully prior to transplant (i.e., mPAP deceased to <35 mm Hg), could discontinue the pulmonary vascular modulators and be considered hemodynamically cured of POPH.[25]

However, it is currently cautioned that POPH, *by itself*, is not an indication for LT, especially in those with low native MELD score (<15), due to the unpredictable risks and outcomes after transplantation.[26] For those with MELD score >15 and baseline PVR >450 dyne/s/cm^5, wait-list mortality is increased, but transplant risk appears to lessen *if* mPAP can be decreased to <35 mm Hg with acceptable right ventricle function.[27] The latter parameter is perhaps the most important and in need of further study.

TABLE 3. POPH: A CHRONOLOGY OF SELECTED MILESTONES

Year	First Author	Observation/Contribution
1951	Mantz[6]	First case report of POPH; embolic thrombi suspected from portal system
1960	Naeye[57]	Series of six POPH cases, some without embolic thrombi; other pathology suggested
1968	Senior[58]	Reported that POPH could follow years after portosystemic shunt surgery
1979	LeBrec[59]	Series of POPH cases suggesting toxic splanchnic bed substances as possible etiology
1983	McDonnell[60]	US autopsy series; 1.5% incidence rate of POPH in cirrhosis
1987	Edwards[61]	POPH autopsy series describing "plexogenic arteriopathy"
1990	Groves[62]	NIH registry of PH; 9% had cirrhosis of the liver
1991	Hadengue[63]	POPH did not correlate with portal hypertension; cardiac output main factor in survival
1991	Robalino[64]	Literature review: 5-year POPH survival rate with "standard" vasodilator treatment was 4%
1993	Yoshida[9]	First report that LT *alone* could not reverse severe POPH
1996	Castro[65]	Mayo series showing LT could be safely done when mPAP < 35 mm Hg
1997	Ramsay[19]	First description of intraoperative deaths during LT because of POPH
1999	Tuder[66]	Pulmonary artery prostacyclin endothelium deficiency in POPH autopsy specimens
1999	Krowka[67]	Mayo series showing IV prostacyclin improved PVR, mPAP, and cardiac output up to 30 months in POPH
2000	Krowka[20]	POPH literature review: pre-LT mPAP > 35 mm Hg a risk factor for post-LT death
2004	Krowka[21]	Multicenter POPH database; 35% mortality rate post-LT if mPAP > 35 mm Hg
2005	Hoeper[68]	German experience using ERA-Bosentan in POPH
2006	Krowka[24]	MELD exception policy initiated; mPAP must be less than 35 mmHg with POPH treatment
2006	Aucejo[28]	First description of PH evolving after LT for HPS
2006	Krowka[69]	Mayo POPH echo/right-heart catheterization screening study; if RVSP > 50 mm Hg, POPH in 66%
2008	Swanson[22]	Mayo Clinic outcomes for POPH; 14% 5-year survival rate if no medical treatment
2008	Le Pavec[70]	POPH in the French PH registry; 5-year POPH survival rate of 68%
2008	Kawut[71]	Clinical risks factor for POPH described
2009	Roberts[72]	Genetic factors in POPH first reported
2009	Simonneau[73]	POPH recognized and classified in the WHO Group I of PH
2009	Koch[29]	Series describing PH *de novo* after LT
2010	Bandara[74]	First report of living donor LT for POPH
2011	Cartin-Ceba[75]	Small series first report ERA-ambrisentan for POPH; normalization of PVR occurred
2011	Talwalkar[76]	Spontaneous portosystemic shunts correlated with severity of POPH
2012	Krowka[23]	US REVEAL registry: 40% 5-year survival rate in POPH with medical treatment only
2014	Goldberg[77]	UNOS POPH MELD exception study: post-LT outcomes for POPH: 3-year survival rate of 64%
2015	DuBrock[78]	Current and proposed medical treatments for POPH summarized
2016	Verma[79]	Multicenter UK LT outcomes in POPH; 42.9% deaths within 5 years of LT
2017	DeMartino[80]	LT safely done if mPAP > 35 mm Hg when PVR/echo of right ventricle normal
2017	DuBrock[27]	UNOS POPH MELD exception study: pre-LT PVR and MELD wait-list death correlates
2018	Reymond[81]	Multicenter French LT outcomes in POPH; 61% normalized PVR post-LT
2019	Nikolic[82]	Bone morphogenetic protein deficiency in POPH/first animal model/biomarker described
2019	Krowka[12]	PORTICO; first randomized, placebo-controlled trial in POPH using ERA-macitentan

SOME FINAL CONJECTURES

We have not identified specific circulating mediators directly linked to either HPS or POPH. Current thinking points toward the lack of a "good substance" emanating from the hepatic veins as the cause for intrapulmonary vascular dilatation (IPVD) in HPS, and the lack of clearance of a "bad substance" that invokes pulmonary vasoconstriction and endothelial/smooth muscle proliferation causing obstruction to flow in POPH. Time and more study will determine whether these ideas are sound.

Interestingly, we have also seen that HPS can *spontaneously resolve* (seen in alcoholic patients with cirrhosis who stop drinking; personal observations). Such resolution has never been reported in POPH, but a fascinating and more concerning "resolution" of HPS has been reported by Aucejo et al.[28] from the Cleveland Clinic. These authors described HPS resolution posttransplant, which *transitioned* into posttransplant pulmonary artery hypertension. The thought has been that the pulmonary vascular pathophysiology of HPS and POPH, respectively, could coexist, and that HPS could essentially "offload" the right ventricle pretransplant at the expense of worsening oxygenation. With posttransplant resolution of vascular dilatations caused by HPS, any obstruction to pulmonary blood flow is now unopposed and manifests itself as evolving pulmonary artery hypertension. This clinical picture, albeit uncommon, has been well documented and necessitated the initiation of pulmonary vasomodulator therapy. As Koch et al.[29] have pointed out, indeed pulmonary artery hypertension (should we still call it POPH?) may evolve *de novo* after LT for reasons that remain unclear.

The historical lessons of HPS and POPH are fascinating and evolving. The possible links (and causative circulating mediators) between these two syndromes remain enigmatic. For those interested in a more detailed chronological perspective of HPS and POPH, Tables 2 and 3 summarize selected key studies and contributions that have led to the current understanding of syndrome pathophysiology and the specific implications for LT.

One final and simple observation should be stressed. Despite the risks in treating and transplanting patients with either HPS or POPH, it remains remarkable that replacement of the liver can result in *total reversal* of the severe dysfunction of a distal organ (e.g., the lungs) that otherwise would have dismal outcomes.

SERIES EDITOR'S POSTSCRIPT

In his fastidious review of the progress that has been made in recognizing and characterizing both HPS and POPH, Michael Krowka has given us a step-by-step account of the history of these two syndromes, since the term HPS was first coined in 1977. Although the mediators of these circulatory abnormalities in the lungs of patients with cirrhosis have yet to be identified, it is tempting to speculate that these syndromes either result from the effects of pulmonary "vasculotoxins" released from the diseased liver into the hepatic veins and hence into the pulmonary arteries, or from the cirrhosis-related deficiency of a pulmonary "vasculoprotective" agent.

Fortunately, this Gordian knot can be cut, so to speak, by a LT surgeon, because liver replacement can cure both syndromes. Very occasionally POPH can supervene posttransplant, sometimes when HPS was present preoperatively. The detailed histories of HPS and POPH that Michael Krowka has labored to provide here will serve us well by giving context to future developments in this field.

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