


# Epoprostenol-associated ascites in pulmonary arterial hypertension

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## Abstract

The development of ascites in pulmonary arterial hypertension (PAH) in the absence of pre-existing hepatic dysfunction is usually associated with decompensated right heart failure or cardiac cirrhosis. Ascites in PAH has rarely been associated with intravenous epoprostenol, a synthetic form of the prostaglandin PGI<sub>2</sub>.

## KEYWORDS

ascites, epoprostenol, pulmonary hypertension

## INTRODUCTION

The development of ascites in pulmonary arterial hypertension (PAH) in the absence of pre-existing hepatic dysfunction is usually associated with decompensated right heart failure (RHF) or cardiac cirrhosis. Ascites in PAH have rarely been associated with intravenous epoprostenol, a synthetic form of the prostaglandin PGI<sub>2</sub>. The postulated mechanisms of this form of ascites include: an epoprostenol-associated high cardiac output state, splanchnic vasodilatation, or increased vascular permeability.<sup>1-5</sup> We describe four cases of epoprostenol-associated ascites in PAH (Table 1), not attributable to decompensated RHF, a high-output state, or primary hepatic failure; in each case, ascites resolved with transition from epoprostenol to other pulmonary vasodilators.

## CASE DESCRIPTIONS

Patient 1 was a 78-year-old female with systemic sclerosis (SSc)-associated PAH treated with tadalafil. Epoprostenol was added 1 year later due to disease progression; uptitration to 37 ng/kg/min was associated with symptomatic improvement and right ventricular (RV) normalization on transthoracic echocardiogram (TTE). Two years later, the patient developed ascites requiring recurrent paracenteses despite aggressive diuresis. Malignancy and infection were excluded, and intrinsic hepatic pathology or portal hypertension were excluded by liver biopsy and hepatic wedge pressure assessment. Right heart catheterization (RHC) demonstrated near normalization of hemodynamics without high output. On the assumption that epoprostenol was the cause of the

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TABLE 1 Clinical characteristics and outcomes of patients with PAH and epoprostenol-associated ascites.

Patient ID	Age	Ethnicity	Sex	Diagnosis	WHO FC	BNP (pg/ml)	Other PAH medications	Epoprostenol Dose (ng/kg/min)	Epoprostenol Duration (months)	RA (mmHg)	mPAP (mmHg)	PAWP (mmHg)	PVR (WU)	CI (m/s <sup>2</sup> )	Clinical outcome
1	78	W	F	SSc-PAH	I	49	Tadalafil 40 mg daily	37	28	1	15	2	2.4	3.6	Epoprostenol transitioned to macitentan and tadalafil; ascites resolved
2	56	W	M	HPAH	III	n/a	Sildenafil 20 mg TID; ambrisentan 10 mg daily	19	6	8	47	5	5.8	3.21	Epoprostenol transitioned to IV treprostini; ascites resolved
3	73	W	F	SSc-PAH	II	88	none	49	45	6	34	12	4.4	2.64	Epoprostenol transitioned to ambrisentan and tadalafil; ascites resolved
4	75	B	F	Sarcoidosis-PH	II	222	Ambrisentan, tadalafil	98.5	72	8	32	16	3.5	3.58	Epoprostenol weaned off and continued on ambrisentan and tadalafil; ascites resolved

Abbreviations: PAH, pulmonary arterial hypertension.

ascites, it was transitioned to macitentan and tadalafil; with this, there was resolution of ascites and continued control of PAH.

Patient 2 was a 56-year-old male with hereditary PAH initially treated with sildenafil and ambrisentan. Due to inadequate response, epoprostenol was initiated 6 months later and uptitrated to 19 ng/kg/min. Shortly thereafter, ascites refractory to diuretic therapy occurred. Malignancy and infection were excluded, and intrinsic hepatic pathology or portal hypertension were excluded by liver biopsy and hepatic wedge pressure assessment. RHC noted improved, although still significantly increased, cardiopulmonary hemodynamics without a high output state. Given the severity of the PAH, epoprostenol was transitioned to intravenous treprostinil. Following the transition, the ascites resolved and treprostinil was uptitrated with long-term control of PAH.

Patient 3 was a 73-year-old female with longstanding SSC-PAH treated with epoprostenol; at 49 ng/kg/min, there was marked symptomatic improvement and RV normalization by echocardiography. Diuretic-refractory ascites subsequently occurred. Malignancy and infection were excluded, and intrinsic hepatic pathology was excluded by liver biopsy. RHC demonstrated markedly improved hemodynamics without high output state; epoprostenol was transitioned to ambrisentan and tadalafil; with this, there was resolution of ascites.

Patient 4 was a 75-year-old female with sarcoidosis-associated PH treated with tadalafil and ambrisentan. Due to progressive disease, epoprostenol was initiated; at an eventual dose of 98.5 ng/kg/min, there was marked clinical improvement and improvement in cardiopulmonary hemodynamics. However, intractable ascites developed; RHC demonstrated near-normalization of cardiopulmonary hemodynamics. Malignancy and infection were excluded and intrinsic hepatic pathology or portal hypertension were excluded by liver biopsy and hepatic wedge pressure assessment. Epoprostenol was weaned off (to only the oral agents), with resolution of ascites.

## DISCUSSION

Intravenous epoprostenol, a synthetic version of the prostacyclin derivative PGI<sub>2</sub>, revolutionized the treatment of PAH after FDA approval in 1995<sup>5</sup> and remains an integral component of many advanced PAH treatment regimens; however, it is not without adverse effects. One uncommon complication is the development of refractory ascites in the absence of cirrhosis or portal hypertension. Although this side effect has occasionally been cited,<sup>1-5</sup> it is usually in the setting of a high output

state from the medication. To our knowledge, this is the largest reported series and the only one to document lack of a high output state and to include tissue sampling to exclude intrinsic hepatic pathology.

The etiology of epoprostenol-associated ascites remains speculative. No clear demographic factors suggest a clear predisposition to ascites development: three of four patients were female, and three of four were white; however, given the small number of total patients, conclusions regarding the role of gender or ethnicity are difficult to ascertain. Additionally, the patients were not taking any medications (other than epoprostenol) previously associated with the development of ascites. Although a high-output state has been well-documented as a complication of epoprostenol therapy, its occurrence is unpredictable and not reliably nor necessarily dose-related.<sup>6,7</sup> None of these four patients had an invasively measured high-output state associated with the ascites, nor were they uniformly receiving a high dose of epoprostenol: doses ranged from 19 ng/kg/min to 98.5 ng/kg/min. Moreover, in all four cases, there was no evidence of grossly impaired RV function or volume overload. Cirrhosis or intrinsic hepatic dysfunction has also been proposed as a mechanism; however, none of these patients had cirrhosis by liver biopsy, nor was any additional hepatic pathology present on biopsy that would otherwise explain the development of ascites. Additionally, by measurement of transhepatic gradients, three of the patients (1, 2, and 4) had no evidence of portal hypertension. Other postulated mechanisms of epoprostenol-associated ascites include splanchnic vasodilation or increased vascular permeability, however, there is little evidence to support these theories.<sup>8</sup> Although all patients in this series were on Veletri initially, ascites has been reported with both Flolan and Veletri<sup>2</sup> suggesting that this is due to the epoprostenol itself, rather than the formulation. Additionally, the lack of background pulmonary vasodilator therapy in Case 3 argues against a causative or contributing role for these oral pulmonary vasodilators.

In addition to a pathologic lack of intrinsic hepatic disease and hemodynamic lack of a high output state or right heart failure, these cases demonstrate the safety and efficacy of a variety of therapeutic modifications after occurrence of presumed epoprostenol-associated ascites. In two cases, patients were successfully transitioned to dual oral pulmonary vasodilator therapy; in one case, the patient was transitioned to IV treprostinil, and in one case, epoprostenol was weaned to the background dual oral pulmonary vasodilator therapy. In all four cases the ascites resolved clinically. Interestingly, in Patient #2, who was transitioned to another prostacyclin analog, ascites also did resolve. This case suggests that, for those patients whose hemodynamics still require parenteral

therapy, intravenous treprostinil may be a safe and effective alternative.

In conclusion, epoprostenol-associated ascites is a rare, but serious, complication of parenteral epoprostenol therapy. The occurrence of ascites in PAH patients receiving epoprostenol should be thoroughly evaluated before attributing it to the epoprostenol. However, if other causes have been excluded, modification of the therapeutic regimen by transition to oral pulmonary vasodilator therapies or to alternative prostacyclin analogs may be a safe and effective option.

### AUTHOR CONTRIBUTORS

**Noah C. Schoenberg:** Conceptualization, data acquisition, and manuscript creation. **Nicole F. Ruopp:** Conceptualization, data acquisition, and manuscript creation. **Raj D. Parikh:** Data acquisition. **Harrison W. Farber:** Conceptualization, data acquisition, and manuscript creation.

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### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### ETHICAL APPROVAL

Written informed consent was obtained from all living case subjects before manuscript submission, and is available for review upon request.

### GUARANTOR

Harrison W. Farber, M.D. will service as guarantor for this manuscript.

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