

# Pulmonary Hypertension with accompanying Pulmonary Arteriovenous Malformations: Diagnostic and Therapeutic Considerations

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## Abstract

Given the various contributors to the development of pulmonary hypertension, the need to differentiate between alternate aetiologies is crucial. We describe a young female patient with evidence of pulmonary arterial hypertension, as well as co-existing pulmonary arteriovenous malformation, in the absence of clinical criteria consistent with hereditary haemorrhagic telangiectasia. Despite the potential deleterious effects of pulmonary vasodilator therapy the patient improved following initiation of bosentan and sildenafil therapy. The complex issues in management of this patient are discussed.

## Keywords

Pulmonary arterial hypertension; Pulmonary arteriovenous malformation; Endothelin receptor antagonist; Bosentan; Sildenafil

## Introduction

Accurate diagnosis of the underlying aetiology of pulmonary hypertension is important to ensure initiation of appropriate therapy. The emergence of specific therapies for pulmonary arterial hypertension (PAH), along with anticoagulation, has allowed for improvement in prognosis for patients with PAH, however these therapies may aggravate symptoms in pulmonary hypertension secondary to alternate causes. The possible contribution of elevated pulmonary blood flow states is important, due to the potential therapeutic role of percutaneous and surgical procedures and deleterious effects of pulmonary vasodilator agents. We present a complex case in which these competing considerations play a critical role in determining optimal therapy of pulmonary hypertension.

## Case Presentation

A 20 year old woman presented with a 9 day history of cough and dyspnoea with associated chest heaviness and palpitations. This was accompanied by reduced effort capacity to 10 metres. There was no significant past medical history.

On examination there was a parasternal impulse, a loud pulmonary component of the second heart sound, and a systolic murmur extending into early diastole at the apex. Oxygen saturations fell to

92% on minimal exertion.

Chest x-ray demonstrated possible left ventricular failure, enlarged pulmonary arteries and right-sided cardiac chambers. Pathology investigations were unremarkable, with no anaemia noted. Transthoracic echocardiogram demonstrated a moderately enlarged right ventricle with pressure overload and moderate right atrial enlargement. Pulmonary artery systolic pressure (PASP) was estimated at 150mmHg by continuous wave Doppler interrogation of the tricuspid regurgitant jet. The main pulmonary artery and branch arteries were severely dilated. There was no evidence of underlying congenital heart disease or intra-cardiac shunt. The left heart size and function was normal. Computed tomography pulmonary angiogram (CTPA) excluded acute pulmonary emboli.

The patient was transferred to a tertiary centre with a provisional diagnosis of idiopathic pulmonary hypertension, commenced on bosentan 62.5mg twice daily, provided supplemental oxygen and anticoagulated. The patient promptly improved, with repeat echocardiography three days later demonstrating an estimated PASP of 85mmHg.

Further detailed physical examination documented a large telangiectasia on her shoulder, and a pancardiac murmur at the apex. The previously performed CTPA was reviewed and an arteriovenous malformation (AVM) was noted in the lingular segment of the left lung (Figure One) with anticoagulation ceased due to concerns regarding the risk of intrapulmonary haemorrhage. A 100% inhaled oxygen shunt study demonstrated a shunt of 8%.

Subsequent right heart catheterisation results are outlined in table one with pulmonary angiography demonstrated in figure two. Vasodilator challenge with inhaled nitric oxide demonstrated a lack of acute response. Embolization of the pulmonary AVM was deferred due to concerns of precipitating fatal PAH and given the perceived lower risk of stroke and cerebral abscess in the presence of elevated pulmonary pressures. Magnetic resonance imaging (MRI) of the brain revealed several scattered AVM, involving small vessels only. Contrast enhanced computed tomography of the liver did not demonstrate any vascular abnormalities. Given concerns regarding the risks of pulmonary AVM embolization, the presence of increased pulmonary vascular resistance during cardiac catheterisation and limited alternative therapeutic options and previous successful use of specific pulmonary hypertension therapies, a continued trial of endothelin receptor antagonist was recommended.

The patient was continued on bosentan. On follow-up at 3 months World Health Organisation (WHO) functional class had improved from III to II, and six minute walk test (6MWT) from 210m to 474m. The bosentan dose was increased to 125mg twice daily and at 6 months there were further symptomatic improvements with 6MWT of 583m.

Three years following presentation elevation in pulmonary pressure and pulmonary vascular resistance was noted on serial assessments. Sildenafil was commenced at 25mg three times a day. After five months of combination therapy her WHO functional class was I-II with a 45m increase in 6MWT. After twenty-two months on combination therapy, the patient remains asymptomatic (functional class I) with no exercise limitation.

## Discussion

This case outlines difficulties in managing pulmonary hypertension and associated co-morbidity,

with complex decisions regarding pulmonary vasodilator therapy, anticoagulation and the role of pulmonary AVM embolisation.

Pulmonary arterial hypertension is characterised by a progressive increase in pulmonary vascular resistance with progression leading to right ventricular hypertrophy and failure. The emergence of specific therapies has resulted in improved outcome for patients with PAH, however, certain patient subgroups are less likely to improve with therapy with accompanying pulmonary disease limiting the potential benefit and in fact be associated with clinical deterioration. In patients with underlying pulmonary disease, pulmonary vasodilatation resulting in improved flow to poorly ventilated lung segments, which may result in worsening hypoxaemia. Similarly, the use of these agents in patients with pulmonary AVM may result in increased right to left shunt and worsening symptoms. Pulmonary hypertension in a patient with pulmonary AVM, such as in patients with hereditary haemorrhagic telangiectasia (HHT), may complicate a high output state, noting HHT may also be associated with elevated pulmonary vascular resistance<sup>1</sup>. Limited data for the use of pulmonary vasodilator therapies is available from the use of these agents in patients with HHT with the successful use of bosentan and sildenafil (alone or in combination) previously described in case reports [2-4].

Pulmonary AVM may be associated with high risk of stroke and cerebral abscess (11.3% and 9%, respectively) with the risk independent of pulmonary AVM symptoms and severity [5]. This risk is lower in those with pulmonary AVM and associated PAH, with risk declining further as pulmonary artery pressures increase [5]. Pulmonary AVM embolization reduces the risk of stroke and cerebral abscess<sup>5</sup>. While haemoptysis may also complicate pulmonary AVM, and may potentially be fatal [6], the data to support prophylactic embolization to reduce risk of haemoptysis is lacking. Of note, severe PAH is typically regarded as a relative contraindication to AVM embolization [7]. Reassuringly, no consistent increase in pulmonary pressures following AVM embolization was found in a case series excluding those with severe PAH<sup>8</sup>, however, pressures did increase in some individuals, which was not predicted by results of balloon test occlusion. The use of pulmonary vasodilator therapies in patients with pulmonary AVM is relatively limited, in part due to concerns regarding increasing pulmonary blood flow. Bosentan has been used in a similar fashion to our patient described with successful use in a patient with a background of HHT and a combination of pulmonary hypertension and pulmonary AVM. In our case, the presence of an elevated pulmonary resistance as the predominant contributor to pulmonary hypertension, rather than a high output state complicating pulmonary AVM, is the likely mechanism of benefit following initiation of pulmonary hypertension specific therapies.

Anticoagulation is usually recommended in PAH due to the presence of in situ thrombosis [9], noting the use of anticoagulation is based on limited data almost exclusively in patients with PAH, with less experience in other forms of pulmonary hypertension. The presence of pulmonary AVM, such as seen in HHT, has been regarded as a relative contraindication to antithrombotic therapies, noting has previous been a poorly studied area. More recent work has suggested that antithrombotic therapy can be used with caution when a strong indication exists [10] with PAH alone felt unlikely to represent a sufficiently compelling indication.

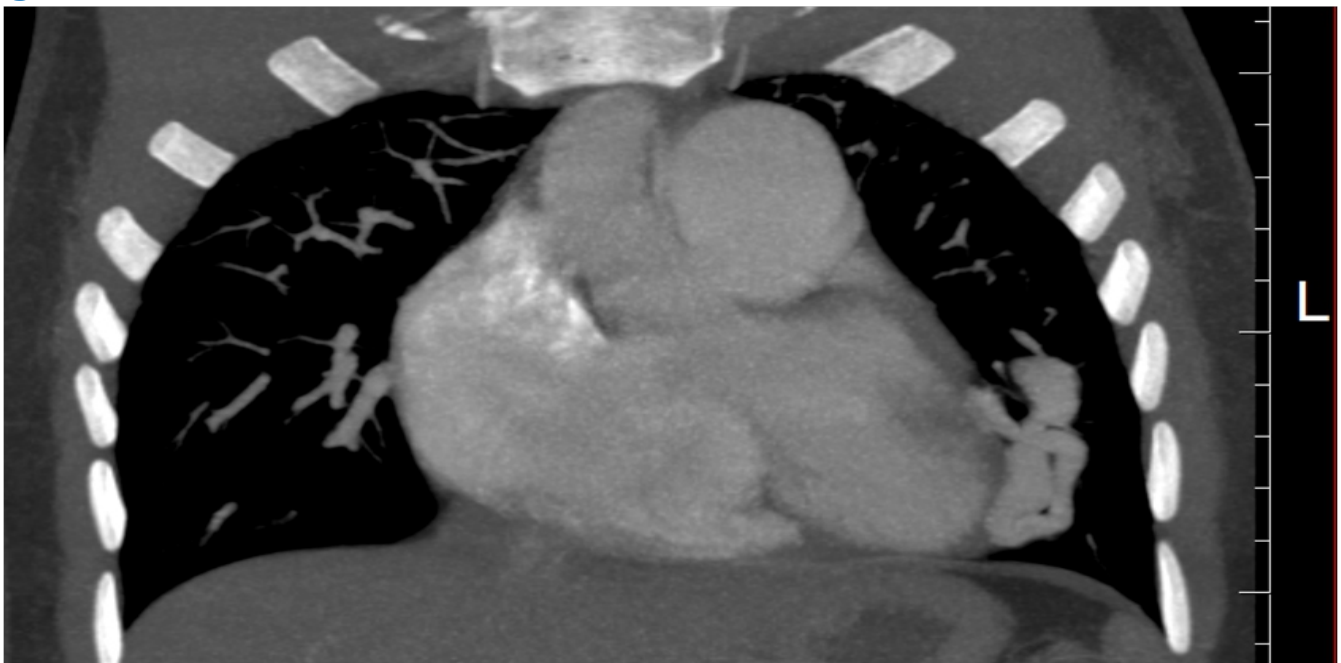
PAH may complicate various underlying conditions, most commonly auto-immune disease, such as the limited cutaneous form of systemic sclerosis (CREST syndrome) [9]. HHT is an uncommon

condition, which may be associated with pulmonary AVM and pulmonary arterial hypertension. The classic description of HHT, also known as Osler-Weber-Rendu disease, is characterised by the development of AVM and telangiectasia in various tissues, including the skin, lungs, brain and gastrointestinal mucosa [11]. While this patient did not demonstrate the typical phenotype, the combination of pulmonary hypertension and pulmonary AVM is illustrative for those caring for patients with HHT. HHT is an autosomal dominant disorder with the PAH phenotype associated with elevated pulmonary vascular resistance in HHT is indistinguishable from that seen in association with the Bone Morphogenetic Protein Receptor type II (BMPRII) mutation associated familial PAH [12]. PAH associated with HHT, however, is due to mutations in the gene coding for ALK1 on chromosome 12 [13,14]. ALK1 associated PAH appears to present at younger age and have a worse prognosis than other recognised mutations causing PAH [15]. Screening for pulmonary AVM is recommended at diagnosis of HHT, given that many are asymptomatic but with a high rate of complications [16]. Transthoracic contrast echocardiography (TTCE) with agitated saline appears to have the best sensitivity whilst being low risk [16]. Physicians performing screening echocardiography for the presence of pulmonary AVM should therefore be aware of the potential for accompanying PAH and alternate underlying causes.

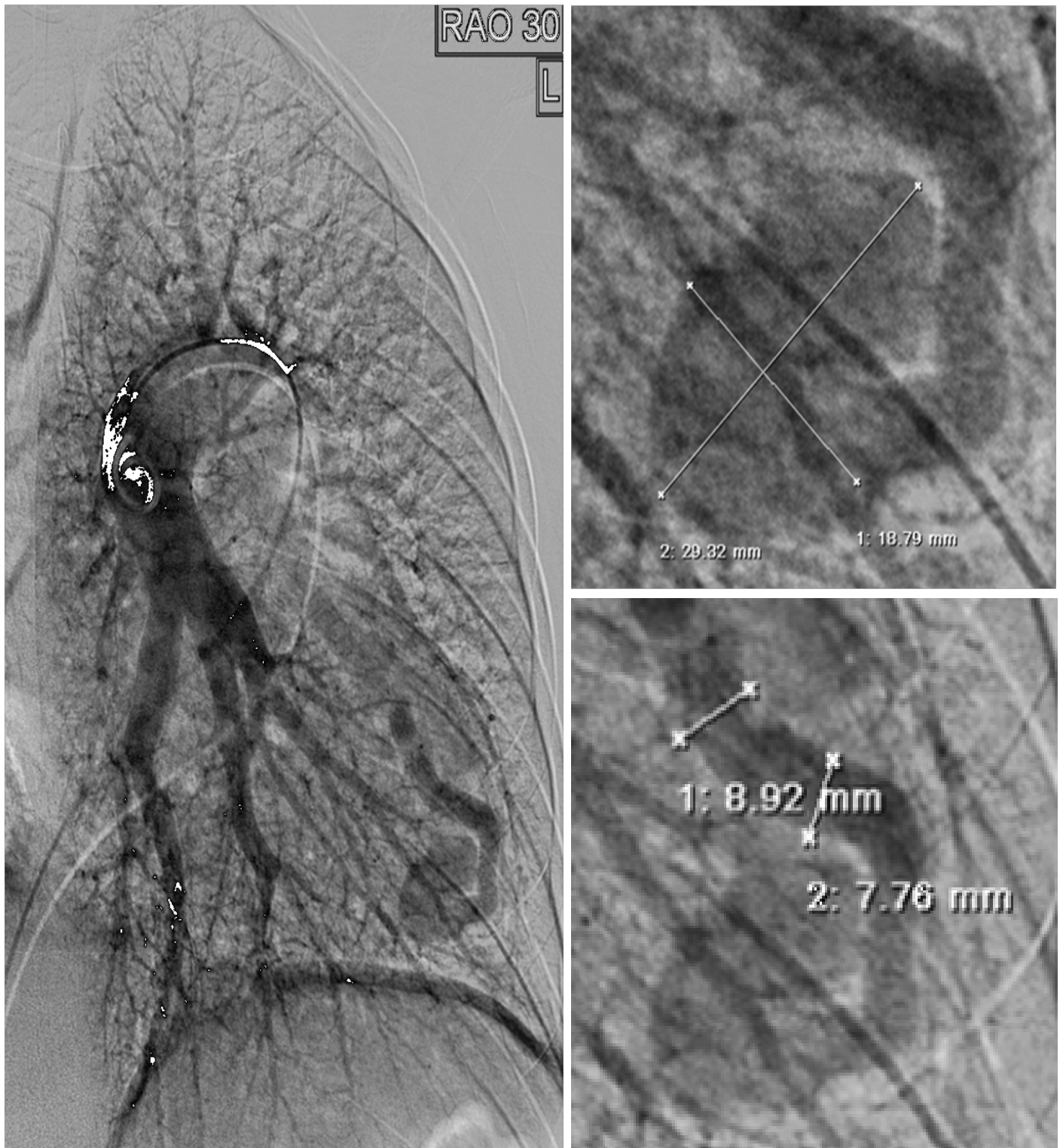
## Conclusion

This patient presented with severe pulmonary hypertension with a large pulmonary AVM noted on imaging and elevated pulmonary vascular resistance documented at cardiac catheterisation. PAH was treated with bosentan with dramatic improvement in exercise tolerance (6MWT) and functional status without complication related to increased pulmonary blood flow in the setting of pulmonary AVM. After 3 years of monotherapy, sildenafil was added with further improvement. The results of this case report add weight to previous reports supporting the use of bosentan and sildenafil in patients with coexisting pulmonary hypertension and pulmonary AVM; this is relevant for patients with HHT in which these conditions may co-exist. The combination of pulmonary hypertension and pulmonary AVM should also prompt formal genetic review with regard to the possible diagnosis of HHT.

## Figures



**Figure 1:** CTPA demonstrating left sided pulmonary AVM.



**Figure 2:** Angiographic images obtained in the RAO projection during cardiac catheterisation demonstrating the location of pulmonary AVM; the size of the AVM and feeding vessel are noted in figures 2b and 2c.

## Tables

	Age	BP (mmHg)	RA (mmHg)	PAP (mmHg)	PCWP (mmHg)	TP Grad (mmHg)	Cardiac Output (L/min)	PVR (dynes-sec/cm <sup>5</sup> )	SVR (dynes-sec/cm <sup>5</sup> )
<b>Sept 2009</b>	20	115/70	12	91/42 (mean 60)	17	43	8	430	809
<b>Feb 2010</b>	21	118/70	10	75/33 (mean 51)	12	39	7.8	400	
<b>May 2011</b>	22	120/62	10	111/40 (mean 70)	12	58	9.9	469	
<b>June 2012</b>	23	121/68	8	95/42 (mean 62)	10	52	7.2	578	

**Table 1:** Right heart catheterisation results

RA = right atrial pressure, PAP = pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, TP Gradient = Transpulmonary gradient, CO = cardiac output, PVR = pulmonary vascular resistance, SVR = systemic vascular resistance

	Aug 2009 <sup>1</sup>	Oct 2009 <sup>2</sup>	Feb 2010	Oct 2011	June 2012 <sup>3</sup>	Nov 2012	April 2013	March 2014
<b>Distance</b>	210 m	474 m	583 m	630 m	600 m	645 m	695 m	675 m
<b>Av Speed</b>	2.1 km/h	4.74 km/h	5.83 km/h	6.3 km/h	6 km/h	6.45 km/h	6.95 km/h	6.75 km/h
<b>Rests</b>	3	0	0	0	0	0	0	0
<b>Max Sats</b>	96%	95%	95%	98%	95%	n/a	96%	n/a
<b>Min Sats</b>	91%	81%	87%	76%	84%	n/a	86%	n/a

**Table 2:** 6 Minute Walk Test

1 Bosentan commenced at 62.5mg BD, 2 Bosentan increased to 125mg BD, 3 Sildenafil 25mg TDS added to Bosentan, n/a = data not available

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