Imaging in pulmonary hypertension, part 1: clinical perspectives, classification, imaging techniques and imaging algorithm

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ABSTRACT
Pulmonary arterial hypertension (PAH) is an uncommon condition associated with significant morbidity and mortality. It has diverse aetiology with differing clinical presentations, imaging features and treatments that range from surgical treatment of proximal chronic thromboembolic disease to targeted medical therapies in small vessel disease. Current classification of pulmonary hypertension (PH) is clinically based and groups diseases with similar pathophysiological mechanisms and therapeutic approaches. Groupings include conditions characterised by diffuse small vessel diseases such as idiopathic PAH, PH secondary to chronic hypoxic lung disease, left sided cardiac disease, chronic large vessel obstruction such as chronic thromboembolic disease and a miscellaneous group of diseases. The physiological manifestation of all of these diseases is increased pulmonary vascular resistance and PAH and while clinical features may provide a clue to diagnosis imaging plays a fundamental role in establishing a precise diagnosis and therefore guides therapy. A broad range of imaging modalities is available for the patient with suspected PH including chest radiograph, echocardiography, ventilation/perfusion scintigraphy, catheter pulmonary angiography as well as cross-sectional CT and MRI. Each modality has its strengths and limitations and different techniques may be used at different stages of diagnostic investigation and frequently complement each other. For example, while MRI and echocardiography permit cardiac structural and functional assessment, CT pulmonary angiography provides exquisite morphological information about the proximal pulmonary vasculature and lung parenchyma but little functional information. Modern cross-sectional imaging techniques (CT and MRI) hold the promise of a comprehensive evaluation of the heart, circulation and lung parenchyma in PH. The authors present a multimodality-imaging algorithm for the investigation of patients with suspected PH though it is acknowledged that there is some variation in practice depending on availability of resources and expertise.

INTRODUCTION
Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (MPAP) of 25 mm Hg or more at rest as assessed by right heart catheterisation.1 Pulmonary arterial hypertension (PAH) is characterised by the presence of precapillary PH in the absence of causes of postcapillary PH such as left heart disease with a pulmonary capillary wedge pressure (or left ventricular end diastolic pressure) of 15 mm Hg or less. Recent systematic reviews suggest that normal MPAP at rest is in fact $14\pm3$ mm Hg with 20 mm Hg being the upper limit of normal.2,3 The significance of an MPAP between 21 and 24 mm Hg is unclear. It has also been demonstrated that normal individuals can achieve MPAPs of much more than 30 mm Hg on exercise, particularly older individuals.4 Therefore, absolute values for pulmonary vascular resistance and a pressure threshold for exercise have been removed from the current definition.5

PH is a significant cause of mortality and morbidity but commonly presents with nonspecific clinical signs and symptoms. Progressive disease leads to right ventricular failure and ultimately death. Causes of PH are diverse. The most common causes are secondary to either chronic left sided cardiac or pulmonary disease. Disease primarily characterised by narrowing of the small vessels results in increased pulmonary vascular resistance and PH; increased understanding of the underlying biology of these diseases has led to a range of effective novel targeted therapies. Obstruction of the large vessels particularly by chronic thromboembolic disease is increasingly recognised as a cause of PH. Patients in whom the distribution of disease lies predominantly in the proximal vasculature may be suitable for surgical pulmonary endarterectomy with the potential for symptomatic and physiological cure.

It is clear that an accurate and early diagnosis of PH and its cause are important to guide therapeutic decision-making. Imaging plays a fundamental role. We describe the clinical signs and symptoms of PH, explain the current PH classification and illustrate various imaging techniques that are available to investigate this condition. The strengths and weaknesses of each of these techniques will also be highlighted.

CLINICAL PRESENTATION
Presenting symptoms are often non-specific which usually leads to a delay in diagnosis averaging about 2 years or indeed misdiagnosis.5 Symptoms are initially those of exertional dyspnoea, but then as the right ventricle (RV) heart becomes increasingly compromised, patients can suffer from reduced exercise tolerance, fatigue, exertional chest pain and syncope. The physical signs include jugular vein distension, left parasternal heave, an accentuated pulmonary component of the second heart sound, a pansystolic murmur of tricuspid regurgitation, hepatomegaly, ascites and pedal oedema. Depending on the cause of the PAH, there may be...
other associated signs such as Raynaud’s phenomenon in connective tissue disease. The prognosis in PAH depends on several factors, notably the underlying cause and severity, but any time lag to diagnosis will also play a part. Ultimately, the magnitude of the increase in pulmonary vascular resistance and any time lag to diagnosis will also play a part. Ultimately, the magnitude of the increase in pulmonary vascular resistance and any time lag to diagnosis will also play a part.

### Classification of PH

Classification of any disease, whether by anatomical site, pathophysiological mechanism or clinical presentation, aids in making the diagnosis and treatment. There have been multiple changes to the PAH classification over the last few decades. The initial 1973 version by WHO, whereby PAH had only two categories, primary or secondary (depending on the presence or absence of any identifiable cause or risk factor), has long since been refined. Since then, there have been three World Symposia on PAH in: (1) Evian, France (1998), (2) Venice, Italy (2003) and most recently (3) Dana Point, California (2008). The current classification (box 1) maintains the general organisation of previous classifications but incorporates additional information published over the last 5 years and also provides more clarity on some specific points. The general aim is to group according to similar aetiology and therapeutic options.

The most recent modifications in the Dana Point Classification include: replacement of the term familial PAH by heritable PAH because specific gene mutations have been identified in sporadic cases with no family history. Heritable forms of PAH include IPAH with germline mutations and familial cases with or without identified germline mutations. Pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis have been included in a new subgroup of Group 1, that is, Group 1’, the reason being that although they are distinct diseases in themselves, they do share similarities with IPAH and should not be completely separated from the PAH group. Schistosomiasis and chronic haemolytic anaemia appear as separate entities in the subgroup of PAH associated with identified diseases. The literature indicates that these conditions can have similar histological findings to IPAH, including pleuroparenchymal fibrosis.

### PH: Imaging Techniques

In addition to laboratory blood tests, ECG, pulmonary function tests and functional assessment, imaging plays a vital role in the preparation for investigation of PH. This includes the detection, characterisation and monitoring of PH. Imaging tests can be

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**Box 1 Updated clinical classification of pulmonary hypertension (Dana Point, 2008)**

1 Pulmonary arterial hypertension (PAH)
   1.1 Idiopathic PAH
   1.2 Heritable
      1.2.1 BMPR2
      1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
   1.2.3 Unknown
   1.3 Drug-induced and toxin-induced
   1.4 Associated with:
      1.4.1 Connective tissue diseases
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart diseases
      1.4.5 Schistosomiasis
      1.4.6 Chronic haemolytic anaemia
   1.5 Persistent pulmonary hypertension of the newborn

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

2 Pulmonary hypertension owing to left heart disease
   2.1 Systolic dysfunction
   2.2 Diastolic dysfunction
   2.3 Valvular disease

3 Pulmonary hypertension owing 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 abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 Pulmonary hypertension with unclear multifactorial mechanisms
   5.1 Haematologic disorders: myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumorous obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Main modifications to the previous Venice classification are in given in **bold**.

ALK1, activin receptor-like kinase type 1; BMPR2, bone morphogenetic protein receptor type 2.

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**Figure 1** Chest radiograph in a 45-year-old female patient with idiopathic pulmonary arterial hypertension showing massively dilated proximal pulmonary vasculature and peripheral attenuation of vessels.
invasive or non-invasive, each having their own strengths and weaknesses. The manifestations of PH in general will be described for each of the different modalities with a suggested imaging algorithm. Disease specific features will be discussed in subsequent articles.

CHEST RADIOGRAPHY
The chest radiograph is usually the initial imaging study to be performed in patients with unexplained cardiorespiratory symptoms. Ninety per cent of patients with IPAH have an abnormal radiograph at the time of diagnosis. The features of PH on the chest radiograph include cardiomegaly, right atrial and right ventricular dilatation, and enlarged central pulmonary arteries (figure 1). Pulmonary vessels in PAH are typically dilated centrally and attenuated peripherally (‘pruned’). However, in the presence of a significant left to right shunt the peripheral pulmonary arteries may appear ‘plethoric’ (figure 2). Central pulmonary arterial diameter can be used as a guide to the presence of PH. On the right side, the interlobar artery at the hilum should measure no more than 15 mm in diameter in women and 16 mm in men. The left sided vessels are seen better on the lateral projection and should measure no more than 18 mm from the posterior margin of the artery to the upper limit of the left upper lobe bronchus. Pulmonary arterial calcification can occasionally be seen in PAH but chest radiography is relatively insensitive. The appearance is due to calcific atherosclerosis from severe and prolonged PAH, usually from shunts with high vascular resistance. The chest radiograph is also helpful in excluding pleuroparenchymal lung diseases, although in general in these diseases the degree of PH does not correlate well with the severity of radiographic findings.

ECHOCARDIOGRAPHY
Echocardiography allows structural and functional assessment of the cardiac chambers, and the estimation of pulmonary artery pressure (PAP). It may identify causes of PH such as left ventricular dysfunction, valvular disease and intracardiac shunts. It is readily available, inexpensive, non-invasive and is used in the initial diagnostic preparation for PH and also in the follow-up. Its limiting factors are operator dependency as well as patient related factors such as tachycardia and obesity.

The estimation of PAP is based on the peak velocity of the jet of tricuspid regurgitation, which is found in more than 90% of patients with severe PAH. The modified Bernouilli equation describes the relationship of peak velocity in m/s ($V_{\text{max}}$) and the peak pressure gradient across the valve in mm Hg ($\Delta P$). The equation is: $\Delta P = 4 (V_{\text{max}})^2$. The equation takes right atrial pressure into account, which can be estimated from the diameter and respiratory variation of the inferior vena cava or is often given a value of 5 or 10 mm Hg. The effect of age and body mass index should be taken into account. A tricuspid regurgitant velocity of 3.0 m/s on echocardiography corresponds to an MPAP greater than 30 mm Hg (figure 3).

Although in general these measurements do correlate with invasive measurements of right ventricular pressures, Doppler-derived pressure estimation may be inaccurate in an individual patient. Underestimation and overestimation of PA systolic pressure are common in patients with severe tricuspid regurgitation. In addition, echocardiography is notoriously inaccurate when tricuspid regurgitation is only mild. The use of contrast echocardiography does significantly increase Doppler signal, allowing more accurate measurement of peak tricuspid regurgitation velocity.

Other entities that can be seen on echocardiography are right-sided chamber dilatation, right ventricular hypertrophy, paradoxical septal motion, increased pulmonary regurgitation, short
acceleration time of the RV into the pulmonary artery, pericardial effusion and a dilated pulmonary artery.

The feasibility of exercise Doppler-echocardiography in identifying PAH only on exercise is questionable due to the lack of prospective confirmatory data. Trans-oesophageal echocardiography can also be performed and is particularly useful in identifying shunts, assessing valvular structures and other lesions such as atrial myxomas.

NUCLEAR MEDICINE

Ventilation/perfusion (V/Q) scintigram is mainly performed to identify potentially treatable CTEPH and differentiate it from other causes of PAH. In non-thromboembolic causes of PAH, V/Q may be normal or non-specifically abnormal showing mismatched non-segmental defects in perfusion giving a ‘moth-eaten’ appearance (figure 4). This contrasts with thromboembolic disease where multiple segmental perfusion defects are typically identified with maintenance of normal ventilation, leading to a mismatch of perfusion and ventilation in the affected bronchopulmonary segment (figure 5). V/Q has a high sensitivity (90%–100%) and specificity (94%–100%) in distinguishing between CTEPH and IPAH, and is more sensitive in this differentiation than CT. Its disadvantage is the exposure to ionising radiation and lack of additional anatomical data. Mismatched perfusion defects will also be seen in other causes of PAH that obstruct/infiltrate the pulmonary arteries, such as extrinsic compression causes, large vessel vasculitis and pulmonary veno-occlusive disease, all of which are described later.

CT

CT is of great value in the investigation of patients with suspected PH. A combination of contrast-enhanced pulmonary angiography (CTPA) and high resolution CT (HRCT) enable detailed assessment of pulmonary vasculature and the lung parenchyma. Cardiac morphology and tricuspid regurgitation can be evaluated even on ungated studies. Unsuspected intracardiac shunts such as atrial septal defect can be diagnosed even for the first time in adulthood.

On CT, the pulmonary trunk should not measure more than 2.8 cm at the level of its bifurcation. If it does, this is suggestive of PH with a sensitivity of 69%–87% and a specificity of

Figure 4  Perfusion scintigraphy in a 45-year-old female patient with idiopathic pulmonary arterial hypertension. The four images show the perfusion series with heterogenous perfusion.

Figure 5  Perfusion scintigraphy in a 60-year-old male patient with chronic thromboembolic pulmonary hypertension. The four images show the perfusion series with bilateral segmental perfusion defects.
Alternatively, if the pulmonary trunk diameter exceeds that of the corresponding aorta, then PH must be suspected (figure 6). This method correlates well with MPAP and has a specificity of 92% and a positive predictive value of 93%. However, its sensitivity is somewhat lower at 70% with a low negative predictive value of 44%. This is due to unfolding and dilatation of the aorta particularly in older patients. A recent study attempting to refine this sign with more precise methods in measuring the main pulmonary artery (ie, obtaining the cross-sectional area) was not helpful. An interesting study by Devaraj et al showed that PA dilatation could occur in the absence of PH in patients with pulmonary fibrosis. Some studies have explored the more peripheral pulmonary vasculature in PH. In normal subjects, the diameter of the arteries within the lungs should be less than or equal to that of the neighbouring bronchus, while in patients with PH, increased pressure can lead to dilatation of these vessels. An increase in the segmental artery to bronchus ratio in at least three lobes has been shown to be a reliable indicator of PH. However, there may also be PH related cardiovascular effects that can be easily appreciated on CT including dilatation of the right heart chambers, right ventricular hypertrophy and paradoxical bulging of the interventricular septum (septal bounce) which may result in left ventricular dysfunction.

In severe right ventricular failure, there may be ascites, hepatic congestion and peripheral oedema. Reflux of contrast medium into the inferior vena cava/hepatic veins suggests tricuspid regurgitation (figure 7). Intracardiac shunts and anomalous venous drainage can also be demonstrated (figure 8). As un gated thoracic CT is not acquired at a specific phase of the cardiac cycle and transverse images are not a standard cardiac plane used in echocardiography and MRI, chamber measurements between the modalities may differ. The literature has studies that do and do not show such differences. There are validated figures for CT axial images, the upper limits for the right atrium and ventricle being 35 mm and 45 mm, respectively.

HRCT facilitates the diagnosis of interstitial lung disease and emphysema. Additional findings of lymphadenopathy and pleural abnormalities can also be readily demonstrated depending on the cause of the PH.

MRI
Cardiac magnetic resonance (CMR) imaging is a non-invasive three-dimensional cross-sectional technique that allows detailed assessment of cardiac anatomy and function including shunt quantification. The lack of ionising radiation makes MRI advantageous, particularly in the serial follow-up. Disadvantages include the normal contraindications to magnetic resonance such as pacemaker devices, foreign metallic objects and claustrophobia. Protracted scan time, breath-hold limitation and arrhythmias are other limitations.

The gradient-echo or steady state free precession pulse sequences can be used to construct a cine series of 15–20 frames across the full cardiac cycle. This technique allows wall motion abnormalities, ventricular volumes, ejection fraction and...
myocardial mass to be assessed for either ventricle in the short-axis or transverse plane. Despite suggestion that the inter-study reproducibility of the RV is less than for the LV, CMR is still considered a reliable method for the assessment of RV morphology and function, with a large RV volume and a low stroke volume being independent predictors of mortality and treatment failure. Right ventricular end-diastolic wall thickness has been shown to correlate well with MPAP in IPAH and some cases of secondary PAH. A linear relationship has also been described between right ventricular mass and MPAP in IPAH (figure 9). Cine images also demonstrate the dynamic distortion of the normal shape of the interventricular septum. With raised right ventricular pressures, the interventricular septum flattens and bows towards the left ventricle, with systolic pressures being proportional to septal curvature in patients with PH. Right ventricular delayed hyper-enhancement can be identified in patients with PH and has been shown to correlate with right ventricular dysfunction. The enhancement pattern involves the RV septal insertion points and the interventricular septum with septal enhancement being associated with septal bowing. However, delayed enhancement in the RV insertion point is a non-specific sign and can be seen in many disease entities and some normal subjects as well.

The pulmonary circulation can be assessed visually by three-dimensional gadolinium magnetic resonance angiography and quantified using velocity-encoded cine imaging. Magnetic resonance angiography demonstrates good correlation with conventional angiography and CTPA. Velocity-encoded imaging produces a map of cross-sectional flow in a vessel over time. In patients with PAH, findings include decreased pulmonary artery distensibility, increased retrograde flow and inhomogeneous velocity profiles. Sanz et al showed a strong correlation between the blood flow velocity in the pulmonary artery and the severity of PAH, suggesting that a decrease in pulmonary blood flow velocity is proportional to the increase of pulmonary vascular resistance. A cut-off value of 11.7 cm/s was established to differentiate between patients with and without PAH. Another finding that can be demonstrated on MRI phase contrast sequences is reduced systolic right coronary artery blood flow. In PAH, the peak and mean systolic flows are reduced compared with the diastolic flow. This is due to compression of the right coronary artery by the hypertrophied RV and is directly related to RV mass.

**RIGHT HEART CATHETERISATION AND CATHETER PULMONARY ANGIOGRAPHY**

Right heart catheterisation is required to confirm the diagnosis and pulmonary angiography may also be performed at the same time. It allows assessment of pulmonary haemodynamics, cardiac function and vasoreactivity of the pulmonary circulation. Although invasive, when performed at experienced centres, the morbidity and mortality are low (1.1% and 0.05%, respectively). Multiple variables are recorded including the right atrial and ventricular pressures, mean, systolic and diastolic PAP, and cardiac output. Pulmonary capillary wedge pressure (or the left ventricular end diastolic pressure) is vital to exclude PH due to left heart disease. Oxygen saturation recording is performed to look for shunting as a possible aetiology. Vasoreactivity testing should be performed to identify patients who may benefit from long term therapy with calcium channel blockers. The agent most commonly used is inhaled...
A positive response is a reduction in the MPAP of >10 mm Hg to a value of 40 mm Hg or less, with an increased or unchanged cardiac output. Only about 10% of IPAH patients meet these criteria with about half of these being positive long term responders to calcium channel blockers. Pulmonary angiography is the gold standard technique for defining the anatomy of the pulmonary circulation. It is most useful in the assessment of chronic thromboembolic disease defining the extent and assessing the suitability for surgical intervention (figure 10). It has excellent temporal resolution and is less hampered by motion artefact and venous contamination that is generated with CT and CMR. However, the latter modalities are becoming increasing popular due to their non-invasiveness, ready availability and provision of additional extra-luminal morphologic and/or functional information. In the future, conventional angiography will probably only be performed if an adequate roadmap of the pulmonary vasculature has not been provided by CT or CMR.

**IMAGING ALGORITHM**

Equipment availability, expertise and cost are some key factors that determine the choice of various imaging modalities in the investigation of PH. The protocol given in figure 11 has been shown to be effective and reliable at our institution.
Main messages

- Presenting symptoms of pulmonary hypertension (PH) are often non-specific leading to a delay in diagnosis averaging about 2 years or indeed misdiagnosis.
- Echo is a great tool to screen for patients at risk of PH but can miss mild PH particularly if there is no tricuspid regurgitation.
- Generic imaging features of PH include cardiomegaly, right atrial and right ventricular dilatation, and enlarged central pulmonary arteries.
- Ventilation/perfusion scintigram is mainly performed to differentiate chronic thromboembolic pulmonary hypertension from other causes of pulmonary arterial hypertension.
- Vaso-reactivity testing should be performed during right heart catheterisation to identify patients who may benefit from long term therapy with calcium channel blockers.
- Although pulmonary angiography is the gold standard technique for defining the anatomy of the pulmonary circulation, non-invasive techniques such as MR pulmonary angiography are emerging as an acceptable alternative with the added attraction of being able to provide additional extra-luminal morphologic and functional information.

All suspected patients start with a chest radiograph. If it is abnormal or if there is a high clinical suspicion of PAH based on history, examination, ECG and pulmonary function test, an echocardiography is performed. If the echocardiogram is normal, no further imaging is necessary but if abnormal or equivocal, further investigation is required. If echo features are suggestive of PAH but no non-cardiac cause is found on echo, then a combined CTPA and HRCT is performed. Any further imaging depends on the CTPA findings. When an occult intracardiac shunt is identified, CMR will be helpful for shunt quantification and ventricular functional evaluation. Equivocal CT findings are followed by nuclear scintigraphy to exclude distal thromboembolic disease. If there is proximal CTEPH, additional imaging using MR pulmonary angiography is performed to further define the anatomy and disease extent for the surgeon. Where MR is contraindicated, catheter pulmonary angiography is used as an alternative. All patients have right heart catheterisation for confirming the diagnosis and assessing disease severity. Follow-up post-pulmonary endarterectomy is performed using right heart catheterisation, CTPA and CMR. IPAH is a diagnosis of exclusion.

CONCLUSION

PAH is uncommon but associated with significant morbidity and mortality. It may present late with non-specific signs and symptoms. Imaging plays a pivotal role by identifying specific causes, quantifying disease severity, as well as helping in directing treatment. Since cross-sectional imaging is commonly performed in patients with non-specific cardiopulmonary symptoms, it is important that imagers and clinicians routinely consider whether there are imaging features suggestive of PH. The various modalities play complementary roles in assessment with precise imaging algorithm varying according to local facilities and expertise.

Key references


SELF ASSESSMENT QUESTIONS (TRUE/FALSE; ANSWERS AFTER THE REFERENCES)

1. PH is defined as systolic pulmonary arterial pressure of >25 mm Hg at rest.
2. The size of the pulmonary arterial enlargement on chest radiography correlates well with the severity of PAH.
3. V/Q scintigraphy has high sensitivity and specificity in distinguishing between CTEPH and IPAH.
4. Pulmonary arterial dilatation can be seen on CT in the absence of PH.
5. Catheter pulmonary angiography has better temporal resolution compared with MRI.

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REFERENCES


ANSWERS

1. False: PH is defined as mean pulmonary arterial pressure of >25 mm Hg at rest.

2. False: The size of the pulmonary artery on radiography does not correlate well with haemodynamic severity of PAH.

3. True: V/Q sensitivity is 90%–100% and specificity is 94%–100% in distinguishing these two conditions.

4. True: Pulmonary arterial dilatation can be seen in patients with pulmonary fibrosis without PH.

5. True: Pulmonary angiography remains the gold standard for delineation of the pulmonary vasculature although it is invasive and does not give any functional information.
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