Pulmonary hypertension (PH) is a rare and complex condition characterised by progressive worsening of pulmonary vascular resistance. The consensus definition of PH is an aggregate of haemodynamic factors that include a mean pulmonary artery pressure of greater than 25 mmHg at rest or more than 30 mmHg during exercise, normal pulmonary capillary wedge pressure, pulmonary vascular resistance > 3 Wood units, and normal or reduced cardiac output. This article will highlight the latest classification of PH, its pathogenesis, multimodality imaging features and the various treatment options.

Over the last 35 years, the classification of PH has undergone major reorganisation. For a long time, a simplistic approach was followed, dividing the condition into primary or secondary depending on the presence or absence of risk factors. Subsequent attempts have broadened the classification and cluster disease processes into those with similar pathophysiological mechanisms and therapeutic options. The most recent revision to the classification followed the 4th world symposium on PH in Dana point, California held in 2008. This updated classification is listed in Table 1.

Even though multifactorial causes for PH have been identified and tremendous advances made in the field of therapeutics, the overall prognosis remains poor with approximately 15% mortality within one year. An important exception is chronic thromboembolic disease (CTEPH) for which definitive treatment is available in the form of pulmonary endarterectomy. The factors that determine prognosis include functional class as measured by six-minute walk (6MW) test or cardiopulmonary exercise test, severity of right heart dysfunction and blood levels of brain natriuretic peptide, an increase in the latter is associated with a worse prognosis.

The histopathological changes in all forms of pulmonary arterial hypertension (PAH) share many similar qualitative features but with differences in the disease distribution according to the site of insult. PAH is a panvasculopathy mainly affecting the small pulmonary arteries. General features of pulmonary vascular remodelling include medial hypertrophy, intimal and adventitial proliferation and right ventricular hypertrophy, while pleiromorphic arteriopathy due to focal disruption of the internal elastic lamina and necrotising arteritis form more complex lesions. Recurrent inflammation can be complicated by formation of in-situ thrombosis and dissection of pulmonary arteries. In disease processes that predominantly affect the post-capillary segments, the small veins and venules demonstrate the medial hypertrophy and intimal proliferation with extensive and diffuse occlusion in pulmonary veno-occlusive disease (PVOD). Alternatively, a patchy panlobular microvasculopathy can be seen with pulmonary capillary haemangiomatosis (PCH). PVOD and PCH can also be associated with pulmonary haemosiderosis and interstitial oedema.

Symptoms of PH are generally insidious with non-specific clinical signs. Electrocardiography may show the presence of right ventricular strain but has low sensitivity (55%) and specificity (70%) to detect significant PH. Therefore, imaging plays a pivotal role in the diagnosis, assessment and management of patients with PH. Generic imaging features of PH include a dilated main pulmonary artery, enlargement of right-sided cardiac chambers, right ventricular hypertrophy, paradoxical septal motion and tricuspid regurgitation.

Echocardiography is an important screening as well as a first line diagnostic tool in PH evaluation. This non-invasive test is inexpensive, widely available and can be used as a bedside test without any radiation burden. It provides morphological and functional assessment of right heart chambers and estimation of pulmonary artery pressure using Doppler echocardiography to demonstrate a tricuspid regurgitation jet.

Pulsed wave tissue Doppler imaging and three-dimensional (3D) echocardiography can measure other variables such as right ventricular fractional area change (RVFAC), RV myocardial performance index (Tei index) and tricuspid annular plane systolic excursion (TAPSE). Of these, the Tei index assessing both systolic and diastolic function of the RV has been shown to be of prognostic relevance in PH. Another echocardiographic predictor of mortality is the presence of pericardial effusion. In spite of its many advantages, limitations of echocardiography includes operator dependence and poor acoustic windows.

Chest radiography, multi-detector computed tomography (MDCT), magnetic resonance imaging (MRI), ventilation-perfusion scintigraphy and pulmonary angiography are other imaging modalities that can be used for diagnosing the aetiology, assessment of disease severity and follow up. The utility of each of these techniques is addressed in the forthcoming section.

Right heart catheterisation (RHC) is the gold standard investigation for haemodynamic assessment in PH. Although invasive, it has a good safety profile with a reported procedure...
Cardiovascular disease-related mortality of 0.05%. Cardiac output measured by thermocoupling or Fick principle is used to calculate pulmonary vascular resistance. An important component of RHC is the vasodilator challenge in patients in whom treatment with calcium channel blockers is being considered. A short-acting vasodilator such as inhaled nitric oxide (NO) is used to identify the subset of patients who will potentially respond by reducing in mean pulmonary artery pressure (mPAP) of at least 10mmHg to an absolute mPAP of less than 40mmHg without a decrease in cardiac output. This selective pharmacological intervention of the imaging findings of all the causes of PH listed under the current classification is beyond the scope of this article. Those conditions that have important radiological implications have been preferentially illustrated.

**Idiopathic pulmonary arterial hypertension (IPAH)**

Pulmonary arterial hypertension is a rare condition with an estimated prevalence of 15 per million. Important subgroups of PH include IPAH, familial PAH, PAH associated with conditions such as connective tissue disease, congenital heart disease, portal hypertension, HIV infection and exposure to toxins and drugs. Of these, IPAH formerly labelled as primary pulmonary hypertension affects around six per million. Prognostic figures from the NIH registry estimate the median survival of IPAH to be 2.8 years. Significant advancement in therapeutics in recent years has resulted in survival improvement. The adult French registry data of PAH has demonstrated one-year survival of 88% in the whole incident group and 89% in the subgroup of incident patients with IPAH, familial, and anorexin-associated PAH. The average delay between development of symptoms and the diagnosis of IPAH is two years. In most cases, abnormal PA pressure on echocardiography triggers further investigations. Since IPAH remains a disease of exclusion, the role of imaging is to ensure the absence of any other underlying condition that could be attributed to PH.

A chest radiograph can demonstrate the familiar generic features of PH such as cardiomegaly and enlarged central pulmonary arteries with peripheral pruning (figure 1, but there is no correlation between the extent of the radiographical abnormalities and the severity of pulmonary hypertension.

MDCT provides confirmation of PH by demonstrating enlargement of proximal pulmonary arteries, right-sided chamber dilatation, right ventricular hypertrophy and transient regurgitation (figure 2). Ancillary features of IPAH include abrupt tapering of subsegmental vessels, tortuous “corkscrew” peripheral arteries and heterogeneous parenchymal attenuation due to regional variation in lung perfusion. Thus, the ventilation-perfusion scintigraphy in IPAH patients may demonstrate mottled perfusion but this is quite different to the lobar or segmental defects of CTEPH. In situ thrombosis is seen in about 50% of histological examinations of IPAH. Thrombi can be eccentric and calcified but usually non-occlusive. Diffuse, poorly defined centrifibular nodules have been described in one case series and shown to correspond to cholesterol granulomas in severe PAH. Pericardial effusion or thickening is also present in patients with PAH. Generally, MR imaging is not used for diagnosing IPAH but may well be suited for assessment of right-heart function and serial follow-up after initiation of therapy. A caveat is that most intravenous infusion devices used for administration of prostanoids may not be MR compatible.

Familial PAH is associated with mutations in BMPR2 gene. There are no distinctive imaging features that differentiate inherited PAH and PAH secondary to drugs such as anorexigenics from IPAH.

Treatment of PAH includes general measures such as life style change, oxygen therapy and calcium channel blockers in those who respond to vasodilator challenge. Concomitant anticoagulation should be considered in IPAH as it has been shown to improve survival. There are multiple trials using combination therapy with prostacyclins, endothelin receptor antagonists and phosphodiesterase inhibitors that show varying benefits. These are expensive and not widely available.

**Connective tissue disease (CTD) associated PH**

Several connective tissue disorders such as scleroderma, particularly the limited variant systemic sclerosis and less frequently mixed connective tissue disease, polymyositis, dermatomyositis, systemic lupus erythematosus, primary Sjogren’s syndrome and rheumatoid arthritis are associated with PH. The prevalence of PAH in this group is variable but around 10-15%. The prognosis in patients with CTD associated PAH is worse than for IPAH with median survival in untreated patients of only 12 months.

In these conditions, a vasculopathy similar pathologically to IPAH can develop and cause severe PH even in the absence of CTD associated interstitial lung disease. Chest radiograph can be spuriously normal or show features of interstitial fibrosis. MDCT can be useful to demonstrate the distribution and degree of fibrosis. Fabulous oesophagus and recurrent aspiration are complications that can be seen in systemic sclerosis. Early diagnosis and institution of therapy is crucial as even in the treated group, the prognosis is poor.

**Porto-pulmonary hypertension and PH related to HIV**

Although these two entities are dealt with together as they can occur concomitantly given the shared behavioural risks; however, each disease can occur in isolation. The risk of developing PAH increases with the duration of portal hypertension and also to the duration of HIV. With the latter, PAH is independent of the CD4 count or previous opportunistic infections.

Histological and imaging features of both conditions are similar to IPAH. An additional marker on MDCT for porto-pulmonary hypertension is the presence of porto-systemic collaterals resulting in formation of varices.

Prognosis in HIV related PAH is similar to IPAH while survival in porto-pulmonary hypertension is dependent on severity of cirsorhosis and underlying cardiac function.

**Congenital heart disease**

Approximately 5-10% of patients with congenital heart disease develop pulmonary arterial hypertension. The size and location of intracardiac defects determine the severity of PAH. A left to right shunt will expose the pulmonary circulation to volume and pressure overload resulting in vascular remodelling. Over time, Eisenmenger syndrome characterised by shunt reversal may develop.

Although there are many histological similarities between CHD associated PAH and IPAH, prognosis in the CHD group is much better with three-year survival of around 93% among patients with Eisenmenger’s syndrome. The familiar complex of generic features of PH is seen on the chest radiograph. On serial films, it is important to note the cardiac silhouette, as normalisation can be an indicator of worsening pulmonary vascular resistance. Likewise, the development of ‘normal’ pulmonary vasculature following CTEPH can be a sign of development of shunt reversal. Protracted PAH can be associated with calcification within the pulmonary arteries.

MDCT is not the first line test for CHD. However, unsuspected shunts such as atrial and ventricular septal defects and patent ductus arteriosus can be diagnosed in adults even on non-ECG gated thoracic CT. In Eisenmenger syndrome, there may be secondary PH which can be evidenced by the presence of small serpiginous vessels in the lung periphery that occur due to recruitment of systemic arterial collaterals. Diffuse ill-defined lobular ground glass opacities have also been described in relation to neovascularisation. In addition, there may be multiple enlarged bronchial arteries. In-situ thrombosis can occur due to flow disturbance in the dilated pulmonary arteries (figure 3).

Cardiac magnetic resonance (CMR) is pivotal in the assessment of congenital heart disease and is complementary to echocardiography. Its superior spatial and temporal resolution makes it the non-invasive gold standard for evaluation of cardiac morphology and function. Phase-contrast flow measurements can estimate shunt fractions. MR angiography provides elegant delineation of cardiovascular anatomy. Its high reproducibility and morphological and functional accuracy makes it suitable for serial follow-up. The technique can also be used to identify complications.
and post-operative sequelae. Important limitations of CMR include claustrophobia and contraindications to ferromagnetic compounds.

Where surgical correction is not possible, patients with CHD associated PAH are treated similar to IPAH.

**Chronic thromboembolic pulmonary hypertension (CTEPH)**

The majority of acute pulmonary emboli (PE) resolve without sequelae. In a small proportion of patients, large or recurrent emboli can undergo incomplete recanalisation with endothelialisation and fibrotic obstruction of the pulmonary arteries resulting in chronic thromboembolic disease. Pengo et al found the cumulative incidence of CTEPH to be 1.0% six months after acute PE, 3.1% after one year, and 3.8% after two years. A previous history of acute PE may not be present in up to 60% of patients and 40% lack a prior history of symptomatic venous thromboembolism. CTEPH is more common in women and patients with underlying malignancy. Other risk factors include lupus anticoagulant, splenectomy, ventriculo-atrial shunt and chronic inflammatory bowel disease. The prognosis is poor if untreated with a five-year survival rate of 30% if the mean pulmonary artery pressure exceeds 30mmHg. However, in selected patients pulmonary endarterectomy (PEA), results in substantial improvement of both functional status and long-term survival rate.

The role of imaging in CTEPH is two-fold: (a) to diagnose its presence and (b) to assess surgical suitability.

Chest radiography demonstrates cardiomegaly with enlargement of proximal pulmonary arteries and peripheral pruning. Pleuro-parenchymal abnormalities, including effusions and consequences of pulmonary infarcts such as cavities and scarring may also be present.

Ventilation-perfusion scintigraphy helps in the differentiation of CTEPH from other causes of PH. The presence of one or more mismatched lobar or segmental defects is indicative of thromboembolic disease. However, it is not pathognomonic as conditions such as pulmonary vasculitides, seroma, veno-occlusive disease and fibrosing mediastinitis can also cause perfusion mismatch.

CT pulmonary angiography (CTPA) combined with HRCT offers the possibility of assessing both vascular and parenchymal consequences of CTEPH. CTPA demonstrates dilatation of central pulmonary arteries, eccentric thrombi that lie at an obtuse angle with the vessel wall and may sometimes be calcified, vascular occlusions, abrupt truncation, attenuated distal vessels. Incomplete recanalisation of organised thrombi results in webs and post-stenotic dilatation. Right-sided cardiac chambers are typically dilated with right atrial enlargement. Occasionally, there may be intracardiac thrombi. Reflux of contrast medium into the hepatic veins is a feature of increased right heart pressure and tricuspid regurgitation. Enlarged bronchial arteries can be seen in 50-75% of patients with CTEPH. The presence of bronchial collaterals has been shown to be associated with lower postoperative pulmonary vascular resistance and mortality. Other systemic vessels that can be collateralised include inferior phrenic, intercostal and internal mammary arteries.

Mosaic attenuation pattern is characterised by geographical changes in attenuation with reduced vessel size in the areas of low attenuation in the absence of air trapping. There may be mild bronchial dilatation particularly in the lower zones. Other parenchymal abnormalities include peripheral wedge shaped infarcts, cavities, atelectasis and scarring. Small pleural and pericardial effusions may also be seen in severe CTEPH.

Magnetic resonance imaging is the gold standard for quantification of ventricular volumes and ventricular mass in PH patients. Gadolinium enhanced MR pulmonary angiography can exquisitely demonstrate the vascular changes of CTEPH to segmental level. However, delineation beyond the segmental arteries is superior with catheter pulmonary angiography due to its higher spatial resolution. In our institution, it is now standard practice to use MR rotating 3D maximum intensity projections reformatted from the angiographic dataset as a “road map” in patients being considered for surgery (figure 4). Phase-contrast velocity mapping of ascending aorta and right and left pulmonary arteries is used to measure systemic and pulmonary flows before and after surgery. This technique also allows estimation of bronchial shunting which usually decreases after surgery depending on the extent of revascularisation. Given its accuracy, reproducibility and lack of radiation constraints MR is ideal for serial follow-up and assessment progression and determine response to therapy. There is good correlation between RHC and MR data, making the latter a potential surrogate for the invasive right heart haemodynamics.

Pulmonary angiography is a well-established technique that has been available for many years. However, newer non-invasive imaging such as CT and MR provide assessment both of the vascular lumen and additional morphological and/or functional information. The development of these non-invasive techniques, the use of conventional angiography is restricted, particularly as it carries a small but definite risk. We perform catheter angiography only when CTPA and MR pulmonary angiography are non-diagnostic or contraindicated.

As part of diagnostic workup in our institution, patients with CTEPH who are over 40 years of age undergo conventional angiography to facilitate coronary bypass grafting during the PEA procedure. Although there are no randomised controlled trials, we also routinely insert inferior vena cava filter prior to surgery, as do most large centres that perform PEA.

Pulmonary endarterectomy (PEA) is the definitive treatment but unfortunately not all patients with CTEPH are suitable to undergo the operation. Surgical success is dependent on prudent patient selection, meticulous surgical technique and assiduous postoperative care. To date, the greatest volume of PEA surgery has been performed at the University of California, San Diego (UCSD) whose mortality figures vary between 4.7-10.9%. The key predictors of operative success are preoperative haemodynamic severity and site of disease. High preoperative pulmonary vascular resistance and pulmonary artery pressure, age and higher NYHA functional class are significant risk factors. In patients who have undergone PTE, PVR >500 dynes-sec-cm⁻² in the immediate post operative period have been shown to have higher mortality rate compared with those with post-operative PVR of <500 dynes-sec-cm⁻². Also, PEA is best reserved for patients with proximal thromboembolic disease. Distal disease predominantly involves subsegmental vessels with arte- riopathy of small muscular arteries and arterioles distal to both obstructed and non-obstructed pulmonary arteries. The presence of a high PVR out of proportion to demonstrable morphological disease should raise the suspicion of distal vasculopathy.

Complications in the immediate post-operative period include reperfusion oedema, neurological sequelae such as stroke and re-exploration for bleeding.

Medical therapy is usually palliative and is reserved for specific circumstances such as bridging for surgery and for patients who are at high risk for surgery or with distal disease or those who have persistent PH after PEA.

**Differential diagnosis of CTEPH**

The presence of unilateral proximal arterial obstruction should trigger suspicion of non-thromboembolic conditions that can mimic CTEPH. Of these, pulmonary artery sarcoma is the most ominous. The prognosis is poor, with early surgical resection with PEA offering the only chance of prolonged survival. Although most PA sarcomas are seen in the main pulmonary trunk, tumour can arise in the branch pulmonary arteries, pulmonary valve and right ventricular outflow tract. Ancillary findings such as concomitant lung metastases can be helpful. PET/CT imaging can be useful to demonstrate avid metabolic activity in the tumour.

Large vessel vasculitides such as Takayasu can affect pulmonary arteries in about 15%. The salient features on MRA are the presence of concentric mural thickening along the proximal pulmonary arteries and vascular stenoses. A combination of multiplanar cardiac MRI using T1- and T2-weighted sequences with gadolinium enhanced MRA can also be used for diagnosis and serial follow-up. Wall oedema, mural enhancement and stenosis are well
demonstrated on MRI. FDG-positron emission tomography is also useful in assessing disease activity.

Fibrosing mediastinitis is characterised by mediastinal and hilar soft tissue masses with coarse calcification causing compression and encasement of pulmonary vasculature. The diagnosis is usually established on MDCT.

**Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH)**

These are rare disorders that occur as a consequence of extensive vascular obstruction either in the small veins and venules (PVOD) or capillaries (PCH). The histological features differ from PAH but clinical presentation is similar. It is crucial to identify PVH and PVOD as different entities from PAH as inadvertent administration of vasodilators can result in fatal pulmonary oedema. Both conditions affect young adults with a slight male preponderance for PVOD. The estimated annual incidence of PVOD is 0.1-0.2 cases per million while less than 100 cases of PCH have been reported in the literature.

The haemodynamic hallmark of both disorders is increased pulmonary arterial pressures with normal or low capillary wedge pressure.

In PVOD, the chest radiograph demonstrates features of PH superimposed with signs of pulmonary congestion. Prominent Kerly B lines can be present in the lower zones, a feature of interstitial oedema or peri-venular fibrosis. On MDCT, in addition to general evidence of PH, there is widespread smooth septal thickening and diffuse centrilobular ground glass opacification (figure 5). Ancillary features such as mediastinal lymphadenopathy and pleural effusions can also be present.1 Left atrium is of normal dimension. Number of pulmonary veins can be smaller than usual. MR or catheter pulmonary venography are not routinely performed but if done can show delayed filling of pulmonary veins.

Chest radiograph in PCH may show basal or diffuse reticulonodularity. This is mirrored on MDCT with widespread ill-defined nodularity and diffuse ground glass opacification. Compared with PVOD, there is less septal thickening and miliary nodules are rarely defined.

Overall diagnosis is made using combination of RHC data and imaging findings but histology may well be needed for confirmation. The only curative option is heart-lung transplant with medical therapy only offering palliative support.

**Conclusion**

Pulmonary hypertension is a complex multifactorial disorder with high morbidity and mortality. Imaging plays a cardinal role in establishing a diagnosis, assessment of disease severity and further management. The role of the imaging specialist is magnified in all forms of PH as biopsy is hazardous and histological proof may not be forthcoming.

The radiologist can play a decisive role in establishing the diagnosis and its cause. Since pulmonary hypertension often presents with non-specific cardio-respiratory symptoms and CTPA is a common test in this situation; it is essential that the interpreting radiologist and clinician are systematic in detecting features suggestive of PH and search for any secondary cause. In particular, since CTEPH is currently an underdiagnosed disease which carries a good prognosis when appropriately treated with surgery, features of proximal CTEPH should be specifically sought in all patients with known or suspected pulmonary hypertension.

It is important to have an integrated imaging protocol for PH patients that can prevent unnecessary delay to diagnosis and referral or result in expensive duplication of tests. There is no standardised imaging algorithm for PH as the tests that are performed depend on locally available equipment and expertise. A simplistic diagnostic pathway for PH is proposed in Figure 6. The intricate nature of the disease mandates a multidisciplinary approach to management.

**References**


FIGURE 2
Series of MDCT images from the same patient as figure 1 also demonstrates the familiar complex of PH findings. Top left image shows enlarged main pulmonary artery (MPA) compared with the corresponding ascending aorta (AA). Top right demonstrates enlarged bronchial arteries. Bottom left illustrates enlargement of right atrium (RA) and right ventricle (RV) with right ventricular hypertrophy. Bottom right image shows reflux of contrast medium into inferior vena cava and hepatic veins (arrow) in keeping with elevated right heart pressure.

FIGURE 3
Axial MDCT image in a 38-year-old female with incidental diagnosis of patent ductus arteriosus (PDA). Arrow points to the PDA, a communication between the aorta and left pulmonary artery. Also note the vascular calcification and filling defect within the pulmonary artery (arrowhead) representing in-situ thrombosis.

FIGURE 4
Still image from a rotating 3D MR maximum intensity projection pulmonary angiogram. Image on the left is pre-PEA and shows significant proximal disease on the right. Image on the right is post-PEA and exquisitely demonstrates reopening of the occluded vessels.
FIGURE 5
Axial MDCT images from a 30-year-old male patient with PVOD. There is smooth interlobular septal thickening (arrow) with diffuse ground glass change in the lower lobes.

FIGURE 6
Imaging algorithm for PH.