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Current and Emerging Imaging Techniques in the Diagnosis and Assessment of Pulmonary Hypertension

Abstract

Introduction

Pulmonary hypertension (PH) is a challenging condition to diagnose and treat. There have been many advances in therapies over the last 2 decades,, along with a rapid development of imaging technologies. The increasing availability of non-invasive imaging gives physicians an unrivalled opportunity to improve diagnostic rates and accurately phenotype patients.

Areas covered

This review discusses the role of imaging in the diagnosis, prognostic assessment and follow-up of patients with PH. Imaging methods, ranging from readily available investigations (chest radiography, echocardiography, nuclear medicine and cross-sectional C (CT), to emerging modalities (magnetic resonance imaging (MRI) and positron emission tomography (PET)) are reviewed. The value and limitations of these clinical application of these imaging modalities and their the evidence for clinicalapplication isreviewed.

Expert commentary

Imaging plays a key role in the diagnosis and classification of pulmonary hypertension. It provides valuable prognostic information and increasingly evidence supports serial assessments. The authors anticipate an increasing role for imaging in the pulmonary hypertension clinic. This will reduce the need for invasive investigations, in addition to providing valuable insights that will improve our understanding of disease and allow more targeted approaches to treatment.

Introduction

Pulmonary hypertension (PH) is defined at right heart catheterisation as a mean pulmonary arterial pressure (mPAP) ≥25mmHg [1]. It ranges from often mild elevations of pulmonary artery pressure, frequently seen in the context of cardiac and respiratory disease, to severe elevations of pressure in patients with an underlying pulmonary arterial vasculopathy [2]. Regardless of its aetiology, it has a negative impact on both symptoms and survival. The current classification identifies 5 groups with similar clinical and pathological characteristics; Group 1: Pulmonary arterial hypertension (PAH), Group 2: Pulmonary hypertension due to left heart disease (PH-LHD), Group 3: Pulmonary hypertension due to lung disease and/or hypoxia (PH-lung),Group 4: Chronic thrombo-embolic pulmonary hypertension (CTEPH), and Group 5: Pulmonary hypertension with unclear/multifactorial mechanisms [3]. Key aspects of the management of pulmonary hypertension include establishing the diagnosis of pulmonary hypertension, identifying the form of pulmonary hypertension (which defines the optimal treatment strategy) and the follow-up of patients.

The diagnosis of pulmonary hypertension is usually suggested by an echocardiogram performed in the breathless patient [2], although increasingly the diagnosis is suggested following other imaging investigations, in particular computerised tomography (CT) [3]. Once a diagnosis of pulmonary hypertension is suspected it is important to identify the cause as this defines the optimal treatment strategy [3]. Conditions for which therapies directed at the pulmonary vasculature have been proven to be effective are uncommon (such as PAH and CTEPH). Other forms of pulmonary hypertension, such as PH-LHD and PH-Lung disease, are much more common, but currently for these forms of pulmonary hypertension, treatment is aimed at the underlying disease not the pulmonary vasculature. Diagnostic strategies including confirming the diagnosis of pulmonary hypertension with cardiac catheterisation and the approach to imaging is therefore dependent on the physician ensuring that further investigation is in the best interests of the patient. An important part of this strategy is an appreciation of factors that increase the pre-test probability of identifying forms of PH likely to benefit from therapy. Features from the history are important; a previous history of thromboembolic disease raises the probability of CTEPH. Alternatively, features known to increase the likelihood of PAH such as the presence of an underlying connective tissue disease (e.g. systemic sclerosis, with a prevalence of PAH 9% [4]), portal hypertension (prevalence of PAH 2-6% [4]), HIV (prevalence of PAH 0.5% [4]) should also be sought. In contrast, mild elevation of pulmonary artery pressures, in the context of severe respiratory or cardiac disease, may not require further investigation where there are no red flag features such as, severe elevation of pulmonary artery pressures or severe impairment of right ventricular function.

Imaging plays an important role in the diagnosis and classification of pulmonary hypertension and provides prognostic information. This review describes a number of imaging methodologies that can be implemented in the assessment of suspected pulmonary hypertension.

1 Imaging the cardiopulmonary circulation

1 Chest Radiograph

The chest radiograph is well established as a first line imaging technique for assessment of patients with known or suspected lung disease, providing a general overview of the lungs and pulmonary vasculature. It is helpful in providing a guide to further investigation in patients with unexplained breathlessness, but is insensitive for the detection of pulmonary hypertension, particularly, where pulmonary artery pressure elevation is modest. It provides limited information on potential causes of pulmonary hypertension, but may identify the presence of significant lung disease such as emphysema, pulmonary fibrosis or characteristic changes of sarcoidosis. It is has the advantage that is widely available, utilises minimal doses of radiation and is easily interpreted by medical practitioners. Typical findings in pulmonary hypertension include dilatation of the pulmonary arteries, right atrial and right ventricular enlargement, although the later are features of severe disease. In a historical study of patients with Idiopathic PAH, an abnormality on CXR or electrocardiography (ECG) was found in 90% of patients [4], however, this represents a highly selected population of patients with severe disease and the accuracy of CXR in an unselected population of patients with suspected pulmonary hypertension has not yet been studied.

2 Echocardiography

Echocardiography is widely available and is usually the first non-invasive imaging investigation to suggest a diagnosis of pulmonary hypertension [3]. Echocardiography has the advantage of high temporal resolution with direct visualisation of cardiac motion, allowing assessment of right and left ventricular function and estimation of pulmonary artery pressure, whilst also being portable and easily performed at the bedside. Systolic pulmonary artery pressure can be measured using Doppler echocardiography; The peak tricuspid regurgitant jet velocity (v), measured from Doppler echocardiography, is used to calculate the tricuspid gradient (TG) (pressure difference between right ventricle and right atrium) using the modified Bernoulli equation, $TG=4v^2$. This is then added to an estimate of right atrial pressure to estimate right ventricular systolic pressure, which should be equivalent to systolic pulmonary artery pressure in the absence of pulmonary valvular disease. Right atrial pressure is estimated as either 5, 10 or 15mmHg based on the diameter and respiratory variation of the inferior vena cava [10]. Whilst several studies have identified a strong correlation of echo derived sPAP and right heart catheter measured mPAP in cardiac disease [11,12] the diagnostic utility of echocardiography derived pulmonary artery pressure is less accurate in pulmonary hypertension seen in the setting of respiratory disease. A prospective study of unselected patients with PH, identified the inaccuracies of Doppler echocardiography derived mPAP, with limits of agreement ranging from -40 to 38.8 mmHg [13]. Echocardiographic estimation of sPAP can only be

performed in the presence of tricuspid regurgitation and where this is absent, mean pulmonary artery pressure can also be estimated using systolic time intervals such as pulmonary acceleration time [14,15].

Echocardiography also allows an assessment of cardiac valves and may identify congenital heart defects. The morphological characteristics of chronic right ventricular pressure overload described using echocardiography include flattening of the inter-ventricular septum (IVS), increased thickness of the right ventricular free wall and increased left ventricular eccentricity. In addition, tissue Doppler is helpful in the assessment of diastolic function [16]. Injections of agitated saline (bubble echo) can be used to look for right to left shunting and whether this occurs at an intracardiac or pulmonary level [17,18]. Transoesophageal echocardiography is particularly helpful in the assessment of suspected intracardiac defects such as atrial septal defects which are often not well visualised on transthoracic echocardiography [19].

3 Radionuclide Imaging

Ventilation/perfusion single photon emission tomography (V/Q SPECT) is currently recommended by the European Society of Cardiology (ESC) as the first line screening test for chronic thromboembolic pulmonary hypertension (CTEPH) [18]. The perfusion image entails injection of 100MBq of 99mTc labelled macroaggregated human albumin, exposing the patient to ionising radiation with an effective dose of approximately 0.017mSv/MBq [20]. The macro-aggregated albumin is trapped within the small pulmonary arterioles, and a 3D reconstructed image of the perfusion of the lungs is acquired over around 10 minutes. In CTEPH, characteristic wedge shaped perfusion defects, mismatched to ventilation can be demonstrated. The advantage of this technique over CT is that image interpretation is relatively straightforward and a normal scan excludes the diagnosis of CTEPH. In contrast, the absence of perfusion due to attenuated vessels and the presence of endo-luminal chronic thromboembolic disease may not be appreciated on CT by less experienced observers. Initial studies demonstrated that scintigraphy was significantly more sensitive than CT although more recent studies have demonstrated that in expert hands that CT and 3D MR perfusion techniques are equally sensitive when compared with scintigraphy [21–23]. In addition, imaging of systemic vascular beds (kidneys or brain) can be used to quantify the size of a right to left shunt and can be considered in a patient with unexplained hypoxaemia and pulmonary hypertension [19].

4 Computed Tomography Pulmonary Angiography (CTPA)

Computed Tomography (CT) is the main imaging modality for the assessment of pulmonary parenchymal abnormalities and the most recent guidelines [3] suggest that this investigation should be considered, particularly if there are abnormalities of gas transfer identified on lung function testing. In suspected pulmonary hypertension, a CT

pulmonary angiogram (CTPA) is increasingly performed: a bolus of iodinated contrast is administered typically into the antecubital vein and the scan is acquired ideally at the point of optimal opacification of the pulmonary arteries. CTPA provides information on the pulmonary vasculature and the size of cardiac chambers, and aids identification of the form of pulmonary hypertension. In patients with PAH there are characteristic CT findings, which reflect the severity of pulmonary hypertension [23]. In a large cohort of patients with pulmonary arterial hypertension a systematic assessment of vascular, cardiac, parenchymal and mediastinal features demonstrated characteristic features of various forms of pulmonary arterial hypertension and also identified important prognostic markers [31].

A well-established feature of pulmonary hypertension is an increased diameter of the pulmonary artery (PA). A number of thresholds have been used to identify the presence or absence of pulmonary hypertension. In one study, a transverse PA diameter of >29 mm on CT was shown to have a high positive predictive value (97%) for PH [32] whereas another study used a value of 33 mm [33], and a pulmonary artery with a larger diameter than the adjacent ascending aorta (pulmonary artery-aorta ratio >1) has also been shown to be predictive of PH [32]. In patients where there is a high prevalence of pulmonary hypertension, such as systemic sclerosis, interrogation of the CT can be helpful where an enlarged PA may be the first indicator of the presence of pulmonary hypertension. Dilatation of the PA in this setting, in particular a pulmonary to aortic ratio of >1.0, can be highly predictive [34,35]. CTPA is particularly useful in CTEPH, where the distribution of vascular webs, stenosis and mural thrombus allows for treatment planning and assessment of suitability for pulmonary endarterectomy. Serpiginous vessels within the pulmonary parenchyma are seen in severe pulmonary hypertension, particularly Eisenmenger's syndrome but may also be seen in idiopathic PAH, and are likely to represent neovascularity [28].

Pulmonary hypertension causes remodelling and eventual failure of the right ventricle. Whilst this is visible on CTPA, it is rarely seen in the early stages of disease. CTPA evidence of right ventricular compromise includes dilatation of the right heart chambers, right ventricular hypertrophy (defined as wall thickness of more than 4 mm) and bulging of the interventricular septum towards the left ventricle [40]. Changes of right ventricular hypertrophy are often best appreciated in the right ventricular outflow tract, likely reflecting the reduced quantity of trabeculation. Reflux of contrast into the inferior vena cava and hepatic veins on contrast enhanced CT has been considered to be a marker of the severity of tricuspid regurgitation, commonly seen in pulmonary hypertension [41], often in PH-LHD, although in the authors experience, it correlates poorly with the severity of pulmonary hypertension. In severe pre-capillary pulmonary hypertension such as PAH, CTEPH and PH associated with respiratory disease (where there is severe pulmonary hypertension) the left ventricle is under filled and compressed by the dilated RV, causing a small volume left atrium and ventricle. There may also be features of cardiac decompensation also visible on CT, such as pleural and pericardial effusions, and an increase in inferior vena caval size, all of which are associated with a poor prognosis [31].

Pulmonary parenchymal changes may help to identify the cause of pulmonary hypertension. In patients with pulmonary hypertension due to lung disease, CT can identify the underlying lung disease and monitor changes in severity. Patients with IPAH often have centrilobular ground glass opacities [42] (as shown in figure 2), which have also been described in patients with pulmonary veno-occlusive disease, where additional characteristic features may also be present such as septal lines and lymphadenopathy

[43]. Patients with CTEPH often have regions of sub-pleural scarring from infarction and a mosaic pattern of lung attenuation due to perfusion heterogeneity. Although not in routine clinical use, more specialised methodologies in CT such as ECG gating [44] and dual energy CT for perfusion imaging have been implemented as research tools in pulmonary hypertension [45–47].

5 Magnetic Resonance Imaging

MRI is considered the gold standard for functional and morphological assessment of the heart. Standard sequences implemented in pulmonary hypertension include two and four chamber cardiac cine steady state free precession imaging (SSFP), black blood imaging (dual inversion recovery fast spin echo), contrast enhanced MR angiography and 3D dynamic contrast enhanced MR imaging. Cardiac MRI can be used to diagnose pulmonary hypertension [55,56], assess prognosis and increasingly its utility in follow-up of patients is being assessed.

Cardiac Cine MR Imaging

Retrospectively ECG gated cardiac cine imaging in the two and four chamber views allow for qualitative and quantitative assessment of the structure and function of the ventricles [57]. Segmentation of the ventricular endocardium quantifies the right and left ventricular end-diastolic and end-systolic volumes from which stroke volume and ejection fraction can be calculated. Baseline RV end-diastolic volume and RV ejection fraction and the change in RV ejection fraction over time are both predictive of outcome [58,59]. RV stroke volume measured using cine imaging is less reproducible due to inaccuracies in contouring the ventricles, although new software allowing for thresholding of trabeculation may improve reproducibility. In addition, due to the variable nature of tricuspid regurgitation, RV stroke volume measured by volumetry is a poor reflector of forward pulmonary arterial flow .

The myocardium of the left and right ventricles can be segmented, giving right and left ventricular mass. The ratio of these is the ventricular mass index (VMI = RV mass / LV mass), which correlates with mean pulmonary arterial pressure in patients with pulmonary hypertension [62].

In health, left ventricular pressure is significantly greater than the right ventricular pressure, giving a characteristic circular shape to the left ventricle, and a crescentic shape to the right ventricle on short axis views. The angle of the inter-ventricular septum can be measured, it is increased (deviating towards the LV) in patients with pulmonary hypertension [63]. This has been shown to correlate with pulmonary artery pressure although in the presence of left heart disease septal angle measurements are less accurate due to the confounding effect of elevated left ventricular diastolic pressures.

Functional Imaging of the Pulmonary Artery

Black blood imaging is used to provide a morphological assessment of the pulmonary arteries and aorta. In health, there is high contrast between the flowing blood in the pulmonary arteries (black) and the pulmonary artery wall (high signal/white). A reduction in blood velocity and turbulent flow results in high signal within the pulmonary arteries, a strongly diagnostic and prognostic feature of PH, described as black blood flow artefact.

Phase contrast MRI is a technique that allows for quantification of blood flow. Pulmonary arterial flow, velocity and area change can be calculated and have been shown to have clinical value in the assessment of patients with PH.

Detailed analysis of flow can be obtained using 4D phase contrast flow imaging, in which time resolved 3D datasets of flow are acquired. This can be retrospectively interrogated to analyse flow in multiple regions of interest in the heart or pulmonary vasculature. In pulmonary hypertension, vortices can be seen within the pulmonary artery [64], and the duration of these vortices have been shown to be predictive of the presence of PH [65,66]. Further research examining the clinical utility of 4D flow MRI is warranted.

Contrast Enhanced Angiography and Perfusion Imaging

High spatial resolution 3D images of the pulmonary arteries (contrast enhanced MR Angiogram) can be acquired with the injection of intravenous T1 shortening agents. Typically, a bolus of gadolinium is administered into a large proximal vein (normally in the antecubital fossa) followed by acquisition of a T1 weighted 3D gradient echo dataset, after a delay that has been assessed by a test bolus. This produces high resolution images of the pulmonary vasculature, with good arterial and venous separation, which can be useful in the identification of proximal thrombus [67].

Time resolved Imaging of contrast provides high-resolution angiographic assessment of the pulmonary circulation haemodynamics. These are also particularly useful to assess for right-to-left shunts. Using a lower spatial, but higher resolution acquisition, the dynamic passage of contrast through the pulmonary parenchyma can also be

imaged, with a frame rate of around 0.5s. This data is often presented as the peak signal for each voxel, after the original 'unenhanced' dataset has been subtracted, giving a peak perfusion image [22]. This is particularly useful in the assessment of CTEPH and has been shown to be of equivalent sensitivity to perfusion SPECT imaging [21]. Dynamic contrast enhanced MRI can also be quantified [68–71], potentially allowing for easier longitudinal follow up of perfusion abnormalities in pulmonary hypertension [60]

Magnetic resonance imaging tissue characterisation

Late gadolinium imaging is in common usage in the assessment of patients with myocardial infarction, to assess for myocardial scar tissue [72]. The technique utilizes a T1-weighted inversion recovery sequence performed 10 to 15 minutes after injection of gadolinium (a T1 shortening agent). Normal myocytes enhance early, but wash-out as they do not trap gadolinium, whereas abnormal tissues, such as fibrosis, trap the gadolinium and remain enhanced on delayed imaging [72]. In patients with pulmonary hypertension, late gadolinium enhancement is seen in the right ventricular insertion points and in the interventricular septum [73], it is thought that these areas are exposed to mechanical stress. The extent of right ventricular insertion point and interventricular septal late gadolinium enhancement has been shown to correlate with right ventricular function [74].

A similar pattern of disease can be seen on native T1 mapping (i.e. non contrast enhanced T1 values), with high native T1 values in the RV insertion points [75], which correlates with right ventricular dysfunction [76]. This allows the potential to characterise myocardial tissue, without the use of contrast media and potentially providing a method for the identification of patients at risk of adverse right ventricular remodelling and right ventricular failure.

6 Digital Subtraction Pulmonary Angiography

Digital subtraction angiography (DSA) of the pulmonary artery is an invasive test, in which iodinated contrast is administered through a catheter in the pulmonary artery under fluoroscopic visualisation. DSA is used in many centres in patients with chronic thromboembolic disease to guide surgical intervention [77] and is currently recommended in the ESC guidelines as a final step in the surgical assessment of CTEPH. The advent of CTPA and MR angiographic techniques provide an alternative non-invasive approach to assess suitability for pulmonary endarterectomy. More recently, the authors have demonstrated that in a large population of patients with suspected CTEPH that a first line imaging approach using nuclear medicine imaging, CTPA, 3D perfusion MR and MR angiography can be successfully used to identify patients with CTEPH for pulmonary endarterectomy with a low peri-operative mortality [82].

7 Positron Emission Tomography

Fluorodeoxyglucose (FDG) is a glucose analogue, which is typically bound to 18-Fluorine, a positron emitter. 3D images of the uptake of FDG can be produced using a PET scanner (positron emission tomography), which allows for qualitative and quantitative assessment of tissue glucose uptake and therefore, an assessment of metabolic activity. As the spatial resolution of PET scanning is relatively low, the scan is performed at the same time as CT, for anatomical location. In IPAH, there is significantly increased FDG uptake within the right ventricle and heterogenous uptake within the lung parenchyma [74–76]. In a few centres the availability of PET-MRI scanners allows anatomical location of the uptake on cardiac MRI [86], providing clearer anatomical detail and functional information.

Clinical applications of imaging in pulmonary hypertension

Making the diagnosis of pulmonary hypertension

There are many causes of pulmonary hypertension. The identification of the cause is key in defining treatment: patients with PAH benefit from drug therapy, whilst patients with CTEPH can be potentially cured by pulmonary endarterectomy. The diagnosis may be suggested incidentally by an imaging investigation performed for unexplained breathlessness, such as large central pulmonary arteries on chest radiograph or CT. The diagnostic approach for patients was highlighted in recent ERS/ESC guideline [3], however, the approach is dependent in part on local availability of imaging and expertise.

In the authors' own institution, which is a tertiary PH referral centre for pulmonary hypertension, a multimodality approach is used combining radionuclide imaging, CT, MRI and cardiac catheterisation. As many patients travel long distances for their investigations, a single step approach is taken to reduce the requirement for repeat visits. In other centres, a step-wise approach may negate the need for some of the diagnostic tests.

Prognostic evaluation of patients with pulmonary hypertension

The assessment of prognosis is important in planning treatment, in particular when considering interventions such as initiation of parenteral prostanoid therapy and triggering referral for transplantation. Accurate assessment of prognosis allows for adequate counselling of patients. This assessment is usually based on an assessment of clinical status, exercise capacity and right ventricular function. A wealth of prognostic information can be gained from the clinical status of the patient, and World Health Organisation (WHO) functional class is a useful tool in this regard. A historical study showed that patients with WHO functional class IV had median survival of 6 months, class III had a median survival of 2.5 years and class I and II had a median survival of 6 years [89]. Older age, male sex and poor exercise capacity are associated with a worse prognosis and the cause of pulmonary hypertension also impacts on outcome [90–95]. Right ventricular function may be measured in different ways. Serum levels of NT-proBNP are linked to right ventricular dysfunction, and have been shown to have prognostic value in PAH [94]. On echocardiography, right ventricular function and disease severity can be assessed using tricuspid annular plane systolic excursion (TAPSE) [96], the RV Doppler index [97,98], interventricular septal displacement [99] and with the right atrial area index [99], all of which predict outcome. At right heart catheterisation, a number of measurements can be used to assess prognosis including right atrial pressure, cardiac output/index, stroke volume index and mixed venous oxygen saturation.

Cardiac MRI is also a useful tool in the assessment of prognosis. Multiple studies have identified that stroke volume, RVEF, LV and RV end diastolic volumes are associated with outcome [101,102], particularly when adjusted for age and sex [103]. The strength of RVEF as a predictor of outcome in PAH was highlighted in a recently published systematic review [104]. More recently, a larger study of 576 patients from our centre showed that right ventricular end systolic volume (indexed for age and sex) and pulmonary arterial relative area change were independent predictors of mortality, providing added prognostic value to patient age, sex, subgroup diagnosis and WHO functional class [55]. The presence of a pericardial effusion on echocardiography, CT or cardiac MRI is also associated with a poor prognosis [99], and other features of cardiac decompensation such as pleural effusions and ascites are predictive of a poor outcome.

The challenge facing clinicians is how to incorporate large amounts of data from various imaging modalities and how best to integrate these with other data from the clinic to aid treatment decisions in a way that is meaningful and beneficial to patients.

Follow-up of patients with pulmonary hypertension

A number of parameters are used to assess patients progress including WHO functional class [94], exercise testing measured using field walking tests such as the 6MWT [105,106] and incremental shuttle walking test [107] and widely available blood test such as N-terminal BNP [108,109]. There has been some concern regarding the ability of the 6MWT to reflect changes in pulmonary vascular status and this has led to a drive to explore other markers that are more likely to be sensitive to change. Consequently, there has been a lot of recent interest in cardiac MRI as a highly reproducible, non-invasive, non-ionising tool to assess right ventricular function. Van de Veerdonk and colleagues, showed that cardiac MRI is sensitive to change, with right ventricular volume changes preceding clinical deterioration in apparently clinically stable patients with idiopathic pulmonary arterial hypertension [110]. The same group also showed that changes in stroke volume were a marker of clinical improvement in patients after 1 year of treatment [111]. Further to this, measures of right ventricular function on cardiac MRI have been shown to be highly reproducible [55].

In our centre, we use a multi-modality approach to follow up based on clinical assessment, exercise testing and cardiac MRI to assess response to treatment. Cardiac MRI is not readily available in all centres, so the choice of follow up modality is also based on real life local availability of tests. Echocardiography is an alternative for follow up, able to objectively quantify right ventricular function using TAPSE, right ventricular tissue Doppler and right ventricular free wall strain, although there are concerns regarding the reproducibility of this technique and how it performs as a follow-up tool in routine clinical practice [112–114]. Recently a study has shown that using a simple assessment of symptoms (WHO FC), exercise capacity (6 minute walk test distance) and BNP at follow-up, could be used to risk stratify patients, with no additional benefit provided by performing cardiac catheterisation [82]. In summary, a number of approaches are used in the follow-up of patients, however, the authors suggest that these should include a measurement of symptoms, exercise capacity, right ventricular function and also patient reported outcome measures such as emPHAsis-10 [115].

Conclusion

Imaging plays a key role in the diagnosis of pulmonary hypertension and is increasingly used in the follow-up and monitoring of patients. The last 2 decades have seen significant advances in imaging techniques and a move towards the use of multiple imaging modalities in the assessment of patients with pulmonary hypertension. Despite this, many of the recommendations on the use of imaging approaches are based on expert opinion and studies include relatively small numbers of patients. There is no doubt that given the heterogeneity of pulmonary hypertension that large studies and a move towards standardisation of imaging protocols and international collaboration is required if we are to realise the potential of imaging in pulmonary hypertension. Larger datasets allow for analysis with approaches such as machine learning not only of measurements derived from image analysis, but also inputting the raw images themselves [88]. Using empirical linear regression models [35], or more physiologically linked models [89] may also aid the diagnosis of pulmonary hypertension and refine our approaches to assessment of disease progression and combining imaging metrics with "omics" may pave the way for precision medicine and tailored therapy. Large multi-centre studies examining different diagnostic approaches to the investigation of pulmonary hypertension are lacking and there is only limited data on the cost effectiveness of different approaches to both diagnose and follow-up. Importantly, however, there are a number of ambitious imaging studies on the horizon, and it is important that the pulmonary hypertension community embraces initiatives such as CHANGE-MRI, a multicentre study specifically examining the optimal approach to the diagnosis of CTEPH, if we are going to realise the full potential of imaging.

Key Points

1. Imaging is key in the assessment of patients with suspected pulmonary hypertension.

2. Imaging characteristics can provide important information on the cause of pulmonary hypertension.

3. Non-invasive methodologies such as cardiac MRI and CT can provide useful prognostic information.

4. Cardiac MRI is sensitive to change and reproducible, making it ideal for follow up.

5. Large studies are required to assess the role of non-invasive imaging modalities.

Figures

Figure 1: A series of images from a patient with chronic thrombo-embolic pulmonary hypertension (CTEPH). The top row shows a series of images from a CTPA showing mural thrombus (A and C), a dilated, hypertrophied right ventricle (B) and mosaic pattern of perfusion (D). The bottom row shows a selection of images from the cardiac MRI study with slow flow artefact on black blood imaging (E), dilated, hypertrophied right ventricle on short axis cine images (G), attenuation of vessels on the contrast enhanced MRA (G) and multiple segmental perfusion defects on the perfusion MRI (H).

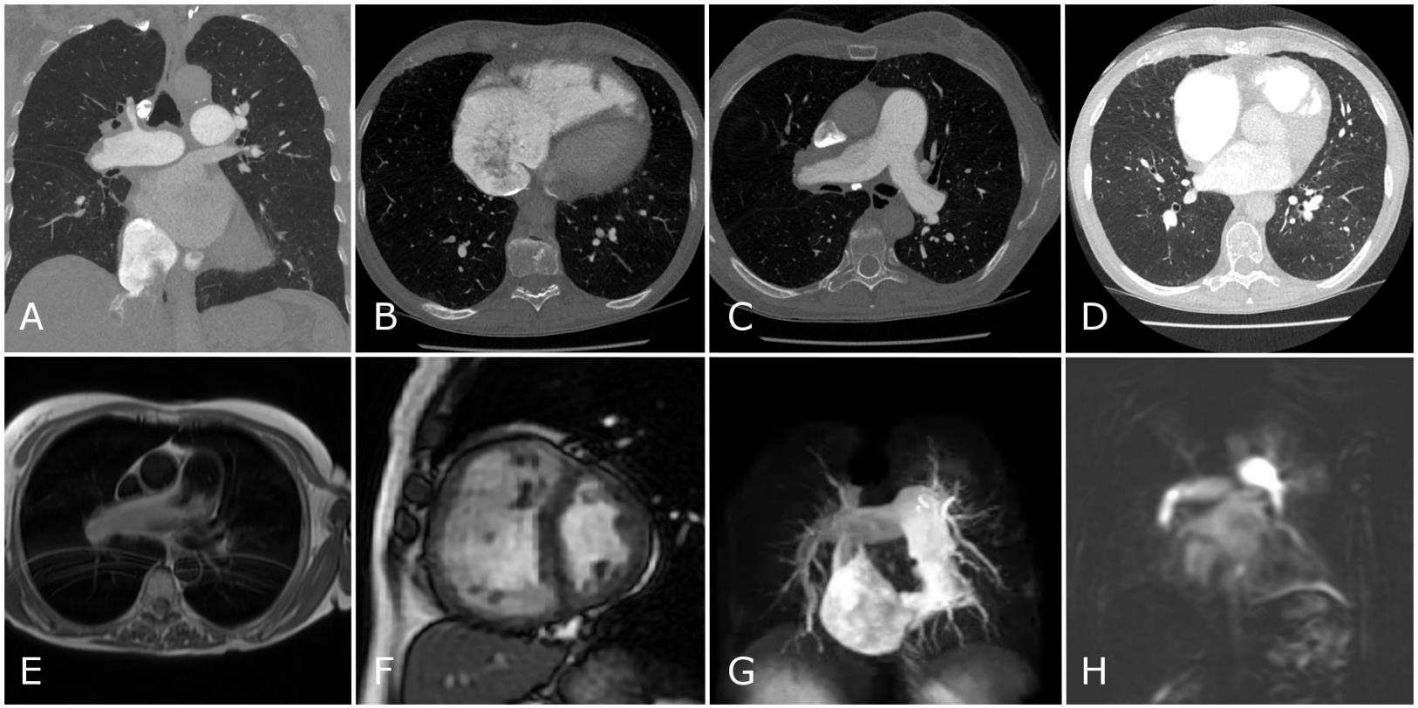
A
B
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Figure 2: Selected image from a patient with idiopathic pulmonary arterial hypertension showing centrilobular ground glass opacities.

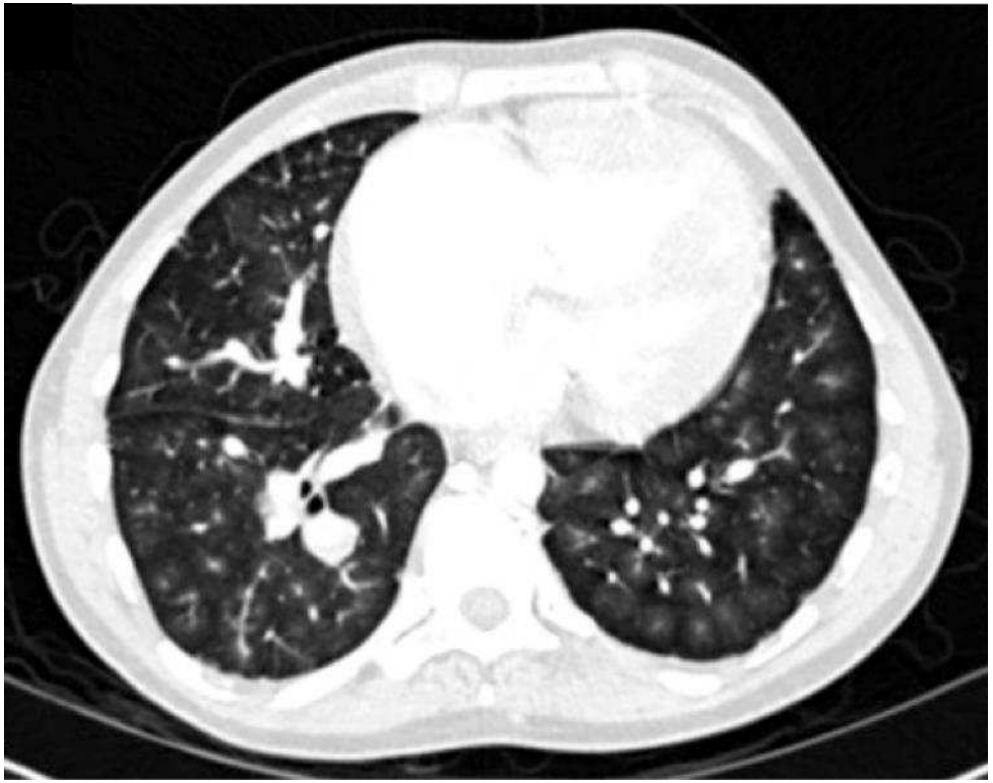


Figure 3: A chest radiograph from a patient with pulmonary hypertension due to left heart disease with combined pre and post capillary disease (A) showing moderate cardiomegaly and upper lobe venous distension. The subsequent MRI shows bi-atrial dilatation (B), flattening of the interventricular septum (C) and slow flow black blood artefact (D). The flattening of the interventricular septum suggests that there is a pre-capillary component to the pulmonary hypertension.

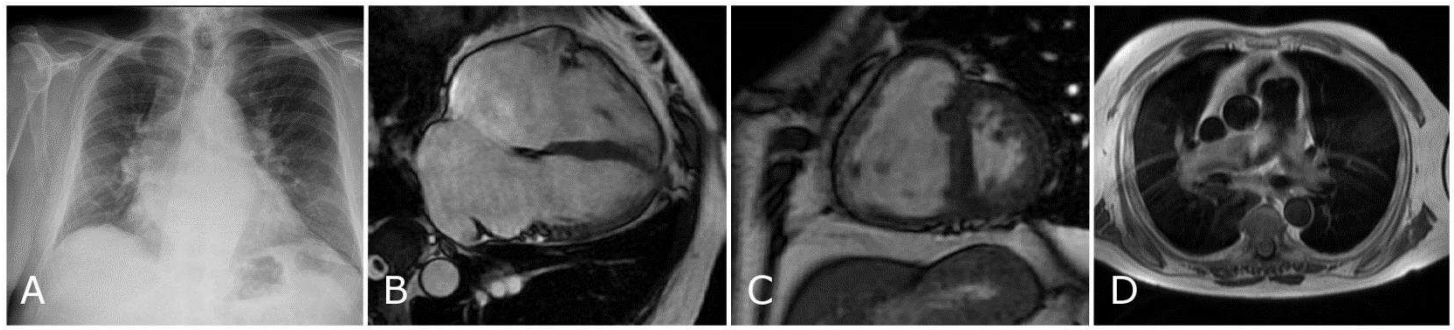


Figure 4: Selected images from a patient with PH due to a patent foramen ovale. The top row (A) shows the images from the time resolved TRICKs, with increasing time to the right of the image. On the early images, there is contrast within the aorta at a time point before filling of the pulmonary arteries, in keeping with a right to left shunt. This was confirmed with quantitative perfusion SPECT over the kidneys (D), which shows uptake of tracer in the capillary bed of both kidneys. The black blood imaging (B) shows dilated pulmonary arteries with slow flow/turbulent blood artefact and the 2 chamber image (C) shows significant flattening of the interventricular septum.

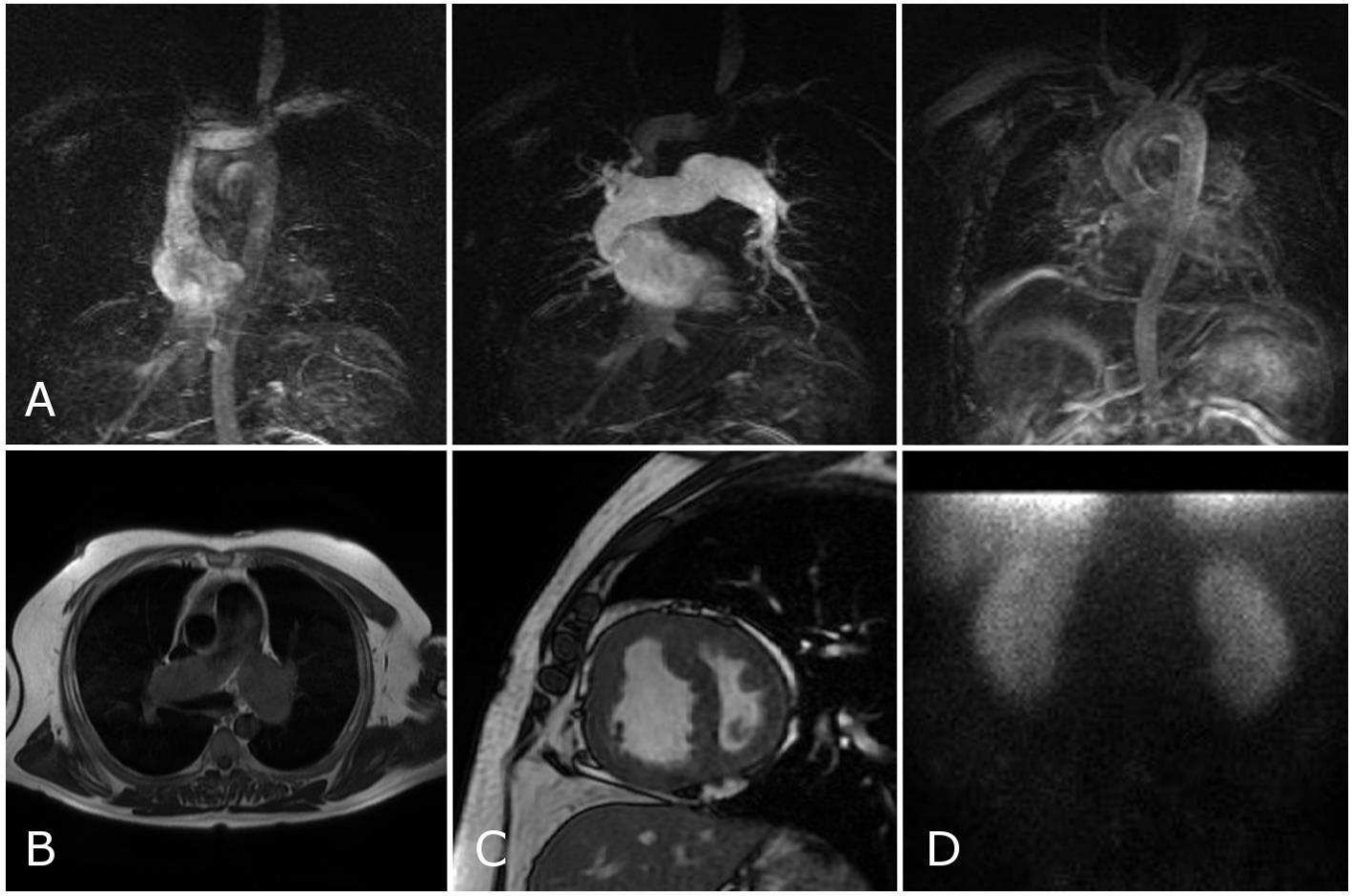


Figure 5: Images from a patient with IPAH. The chest radiograph shows cardiomegaly with dilatation of the pulmonary artery, the patient has a PICC for intravenous delivery of iloprost. Black blood imaging (B) and CTPA (D) confirm the dilated pulmonary artery. Further features of pulmonary hypertension are shown with slow flow artefact on black blood (B), flattening of the interventricular septum (C) and dilatation of the right sided chambers (C and D). Note is also made of poor filling of the left sided chambers and a moderate pericardial effusion.

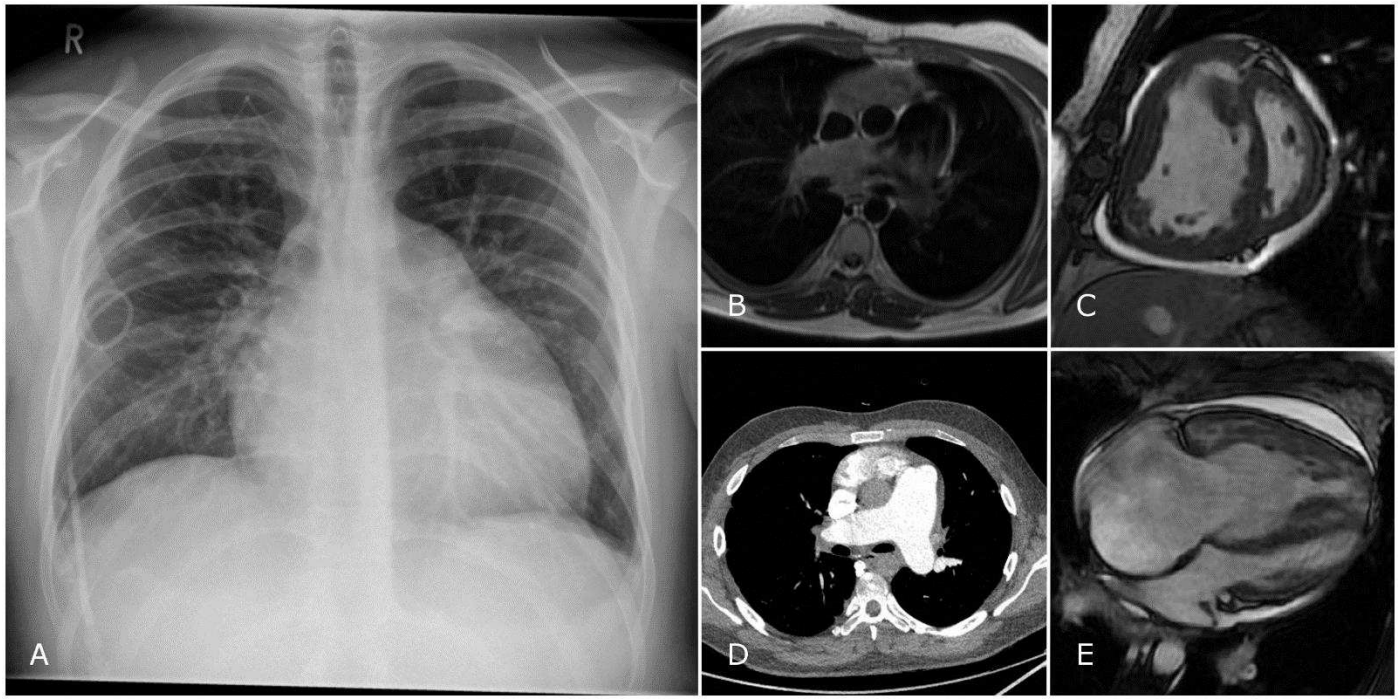
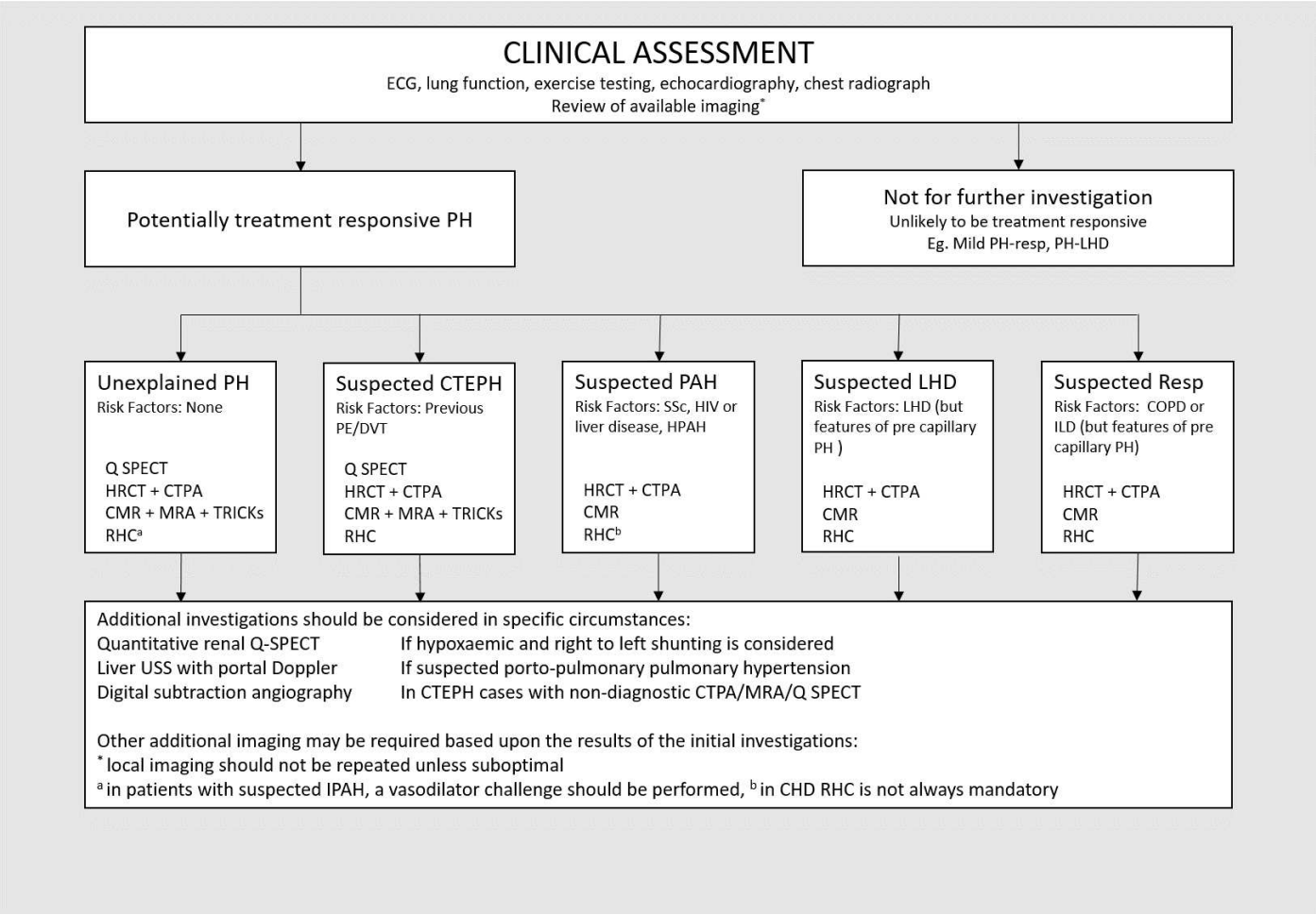


Figure 6: Investigation flow chart in our institution.



	1. PAH	2. Left Heart Disease	3. Lung Disease	4. CTEPH	5. Misc
RHC	mPAP: ↑↑ PAWP: ↔ CO: ↔, ↓ or ↓↓ RA: ↔ or ↑	mPAP: ↑ PAWP:↑ CO: ↔ or ↓ RA: ↑ or ↑↑	mPAP: ↑ PAWP:↔ CO: ↔ or ↓ RA: ↔ or ↑	mPAP: ↑↑ PAWP:↔ or mild↑ CO: ↔, ↓ or ↓↓ RA: ↔ or ↑	mPAP: ↑ or ↑↑ PAWP:↔ CO: ↔, ↓ or ↓↓ RA: ↔, ↑ or ↑↑
CT	PA: ↑ or ↑↑ RV: ↑ or ↑↑ LV and LA:↓↓ Flattened IVS Centrilobular nodules Neovascularity	PA: ↔ or ↑ RV: ↔ or ↑ LA:↑↑ Pleural or pericardial effusions	PA: ↑ or ↑↑ RV: ↑ or ↑↑ Parenchymal lung disease eg. Emphysema or fibrosis	PA: ↑ or ↑↑ RV: ↑ or ↑↑ Chronic emboli: webs, stenoses, mural thrombus Mosaic perfusion	PA: ↑ or ↑↑ RV: ↑ or ↑↑ CT evidence of disease eg sarcoidosis
CMRI	PA: ↑ or ↑↑ RV: ↑ or ↑↑ LV and LA:↓↓ Flattened IVS	PA: ↔ or ↑ RV: ↔ or ↑ LV: ↔ or ↑, LA:↑↑ Septum only flattened in Cpc-PH Pleural/Pericardial Effusions	PA: ↑ or ↑↑ RV: ↑ or ↑↑	PA: ↑ or ↑↑ RV: ↑ or ↑↑ Flattened IVS Chronic emboli on MRA	PA: ↑ or ↑↑ RV: ↑ or ↑↑
V/Q SPECT	No segmental defects Renal uptake in R-L shunt	No segmental defects	No segmental defects Abnormal due to lung disease	Segmental perfusion defects	No segmental defects

, IVS: Interventricular septal angle

Table 2: Diagnostic accuracy for cardiac MRI metrics to predict the presence of PH.

Author	Year	Cases (PH/not PH)	RHC metric	CMR marker	Correlation (R)	Threshold	AUC
Roeleveld [118]	2005	44/0	mPAP	VMI	0.56*	N/A	N/A
Sanz [119]	2007	42/17	mPAP	Average velocity	-0.73**	11.7cm/s	0.90
				Diastolic PA area	0.67**	6.6cm^2	0.95
			PVRI	Average velocity	-0.86**	11.7cm/s	0.92
				Diastolic area	0.64**	6.0cm^2	0.93
Gan [120]	2007	70/16	mPAP	PA RAC	0.47*	N/A	N/A
Garcia-Alvarez [121]	2011	100/0 (80 derivation 20 validation)	PVR	MR estimated PVR	0.84**	≥4.2 WU	0.97
Swift [122]	2012	194/39	mPAP	VMI	0.78**	>0.4	0.91
				LGE present/absent	N/A	LGE Present	0.89
				Diastolic PA area	0.35*	>6cm^2	0.84
Moral [123]	2012	152/33	mPAP	α	0.61**	7.2	0.97
Swift [56]	2013	64+64/12+10	mPAP	Model CMR mPAP	0.82**	≥32mmHg	0.96
			PVR	Model CMR PVR	0.87**	≥3WU	0.94
Johns [124]	2017	87/15 All COPD patients had COPD	mPAP	CMR-RV model	0.689**	32mmHg	0.91
				PA/RV model	0.732**	25mmHg	0.93
				α	0.527**	7.2	0.84
Zhang [125]	2017	50/0 All PAH (25 derivation and validation)	mPAP	CMR mPAP Model	0.647**	N/A	N/A
			PVR	CMR PVR model	0.492**	N/A	N/A

mPAP: mean pulmonary arterial pressure, VMI: ventricular mass index, PVR(I): pulmonary vascular resistance (index), PA: pulmonary artery PA RAC: Pulmonary arterial relative area change, LGE: late gadolinium enhancement, * $p < 0.05$, ** $p < 0.001$

Table 3:

Author	Number of patients	Follow up	CMR metric	Hazard Ratio (confidence interval)
Van de Veerdonk [126]	110 PAH	1 year	Baseline RVEF	0.938 (0.902–0.975)**
			One year ΔRVEF	0.929 (0.875–0.985)*
			RVESVI (ml/m2)	1.014 (1.001-1.027)*
			LVEDVI (ml/m2)	0.962 (0.931–0.994)**
			LVESVI (ml/m2)	0.942 (0.888-0.998)*
Van Wolferen [127]	64 IPAH	1 year	SVI (Phase contrast at pulmonary artery) (ml/m2)	0.32 (0.13-0.84)*
			LVEDVI (ml/m2)	0.31 (0.13-0.81)*
			RVEDVI (ml/m2)	4.2 (1.31-8.30).*
Gan [120]	70	4 years	RAC (%) right main PA	0.87(0.76-0.96)**
Swift [128]	134	20 months	RAC (%) main PA	0.85 (0.74-0.98)*
Hagger [129]	40 PAH-SSc		VMI	N/A – Kaplan Meier analysis
Rajaram [130]			RVEDV	1.02 (1.01-1.03)**
			VMI	5.56 (1.50-35.5)*
Freed [131]	58	10 months	RVIP-LGE	10.0 (1.3 to 77.1)*
Swift [132]	79	2 years	FWHM	1.08 (1.01 to 1.16)*
			PTT	1.10 (1.03 to 1.18)*
Dawes [116]	256	4 years	3D RV motion	2.75 (1.73 to 4.35)**
Swift [55]	576	30 months	RVESVI (%pred)	1.217 (1.06 to 1.54)**
			RAC	0.76 (0.623 to 0.93)**

RVEF: right ventricular ejection fraction, RVESVI: right ventricular end systolic volume index, LVEDVI: left ventricular end diastolic volume index, LVESVI: left ventricular end systolic volume index, SVI: stroke volume index, RAC: relative area change, VMI: ventricular mass index, RVIP-LGE: right ventricular insertion point late gadolinium enhancement, FWHM: full width half maximum, PTT: pulmonary transit time, RV: right ventricle, * $p < 0.05$, ** $p < 0.001$

	Advantages	Disadvantages
Chest Radiograph	Readily available, low cost	Low sensitivity and spe
Echocardiography	Readily available, portable, medium cost	Operator dependent
	Diagnostic and prognostic data	Poor in lung disease
Ventilation/Perfusion SPECT	Higher sensitivity than CTPA for CTEPH	May be non-diagnostic
	Information regarding lung disease	Ionizing radiation
	Easy for non-specialists to exclude CTEPH	
Computed Tomography	Readily available, moderate cost	Exposure to ionizing ra
	Allows assessment of vascular, cardiac, mediastinal and lung structures	Inexperienced radiolog
	Quick to perform	
Cardiac MRI	Gold standard for ventricular function	
	Non-ionizing	High cost, post process consuming
		Not always tolerated, c
Abdominal USS	Non-ionizing	Not specific or sensitiv

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