Published in final edited form as:

J Thorac Imaging. 2014 March ; 29(2): 68–79. doi:10.1097/RTI.0000000000000079.

Quantitative MR imaging of pulmonary hypertension: A practical approach to the current state of the art

Andrew J. Swift, PhD.¹, Jim M. Wild, PhD¹, Scott K. Nagle, M.D., PhD^{2,3,4}, Alejandro Roldán-Alzate, PhD², Christopher J. François, M.D.², Sean Fain, PhD^{2,4}, Kevin Johnson, PhD⁵, Dave Capener, MSc¹, Edwin J. R. van Beek, M.D., PhD⁶, David G. Kiely, MD⁸, Kang Wang, PhD⁷, and Mark L. Schiebler, M.D.²

¹Academic Unit of Radiology, Department of Cardiovascular Science, University of Sheffield, United Kingdom

²Department of Radiology, University of Wisconsin- Madison School of Medicine and Public Health, 600 Highland Avenue, Madison Wisconsin, 53792-3252

³Department of Pediatrics, UW-Madison

⁴Department of Biomedical Engineering, UW-Madison

⁵Department of Medical Physics, UW Madison

⁶Queen's Medical Research Institute, University of Edinburgh EH16 4TJ, United Kingdom

⁷General Electric Medical Systems, Advanced Science Laboratory, Madison, WI

⁸Sheffield Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, United Kingdom

Abstract

Pulmonary hypertension (PH) is a condition of varied aetiology, commonly associated with a poor clinical outcome. Patients are categorised on the basis of pathophysiological, clinical, radiological and therapeutic similarities. Pulmonary arterial hypertension (PAH) is often diagnosed late in its disease course with outcome dependent on aetiology, disease severity and response to treatment. Recent advances in quantitative MR imaging allow for a better initial characterization and measurement of the morphologic and flow related changes that accompany the response of the heart-lung axis to prolonged elevation of pulmonary arterial pressure and resistance and provide a

Corresponding Author: Jim Wild, Academic Unit of Radiology, University of Sheffield, C Floor, Royal Hallamshire Hospital, Sheffield, S10 2JF, UK, Telephone: +44 (0) 114 226 5389, Fax: +44 (0) 114 271 1714, J.M.Wild@Sheffield.ac.uk.

Disclosure Statement:

Andrew J. Swift, PhD - No disclosures relevant to this manuscript

Jim M Wild, PhD - No disclosures relevant to this manuscript

Scott K. Nagle, M.D., PhD. - No disclosures relevant to this manuscript

Sean Fain, PhD- No disclosures relevant to this manuscript

Christopher J. François, M.D. - No disclosures relevant to this manuscript

Edwin Van Beek, M.D., PhD – No disclosures relevant to this manuscript

Dave Capener MSc - No disclosures relevant to this manuscript

David G Kiely M.D – No disclosures relevant to this manuscript

Kang Wang, PhD – Employee of General Electric Medical Systems

Mark L. Schiebler, M.D. - No disclosures relevant to this manuscript

reproducible, comprehensive and non-invasive means of assessing the course of the disease and response to treatment. Typical features of pulmonary arterial hypertension (PAH) occur primarily as a result of increased pulmonary vascular resistance and resultant increased RV afterload. Several MRI derived diagnostic markers have emerged, such as ventricular mass index (VMI), interventricular septal configuration and average pulmonary artery velocity having reported diagnostic accuracy similar to Doppler echocardiography. Furthermore, prognostic markers have been identified with independent predictive value for identification of treatment failure. Such markers include: large right ventricular end-diastolic volume index (RVEDVI), low left ventricular end diastolic volume index (LVEDVI), low right ventricular ejection fraction (RVEF) and relative area change of the pulmonary trunk. MRI is ideally suited to longitudinal follow-up of patients with PAH due to its non-invasive nature, high reproducibility and has the advantage over other biomarkers in PAH due to its sensitivity to change in morphological, functional and flow related parameters. Further study the role of MR imaging as a biomarker in the clinical environment is warranted.

(Mesh Terms) Key words

Pulmonary Hypertension; Pulmonary; Magnetic Resonance Imaging; Multidetector Computed Tomography; Thromboembolism; Heart Catheterization

Introduction

The clinical definition of pulmonary hypertension (PH) is a mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg at rest measured at right heart catheterization (RHC) [1]. RHC is an invasive investigation in which pressure and flow are directly measured by insertion of a catheter via the jugular or femoral vein into the right side of the heart and pulmonary artery. Further detailed assessment using blood testing, echocardiography, lung function and multi-modality imaging is key to identifying the cause of pulmonary hypertension, which defines both prognosis and treatment [2, 3].

The modern classification of PH was introduced 15 years ago with the rationale of bringing together similar conditions on the basis of common pathophysiological, clinical, radiological and therapeutic patterns [1, 4]. There are 5 major forms: Group 1 - Pulmonary arterial hypertension (PAH) which can be idiopathic or associated with other conditions, most commonly systemic sclerosis or congenital heart disease, Group 2 - PH due to left heart disease (PH-LHD), Group 3 - PH due to lung disease and/or hypoxia (PH-Lung), Group 4 – Chronic Thromboembolic Pulmonary Hypertension (CTEPH) and Group 5 - Unclear or multifactorial aetiologies.

PH ranges from an uncommon progressive condition pulmonary arterial hypertension (PAH), which is characterized by a vasculopathy affecting the small pulmonary arteries, to usually mild elevations of pulmonary artery pressure that are more commonly associated with severe cardiac or respiratory disease. In patients with IPAH, prolonged elevation of right ventricular (RV) afterload, results in RV failure and eventually death, occurring typically within 3 years for untreated patients with IPAH [5, 6]. Significant progress has been made in the treatment of IPAH over the last 20 years and the UK and Ireland

Pulmonary Hypertension Registry identified a 5 year survival of patients under the age of 50 at approximately 80 % [7].

Patients with PH usually present with dyspnea and fatigue, with syncope and angina like pain more frequent in advanced disease. Symptoms are non-specific and the delay from initial symptoms to diagnosis is often up to 2 years. As a result damage to the pulmonary arterial vasculature is already quite advanced by the time of diagnosis.

The survival of patients with PAH is dependent on the form of PAH. Hurdman et al, demonstrated the importance of systematic evaluation in 600 treatment naive patients with PAH diagnosed at a PH referral centre with an overall 3 year survival rate of 68%, significantly better in PAH associated with congenital heart disease (85%), compared to IPAH (63%) in turn significantly better than PAH-systemic sclerosis (53%), $p < 0.01$. Kane et al [8] studied important variables associated with outcome in 484 patients and demonstrated that variables associated with poor right ventricular function increased risk of death. Several studies have now demonstrated that a number of haemodynamic and echocardiographic measures associated with impaired right ventricular function identify patient with a poor prognosis including increased right atrial pressure, reduced cardiac index and mixed venous oxygen saturation and reduced TAPSE and severe tricuspid regurgitation) [9, 10].

Van de Veerdonk et al, have shown that baseline measurement of right ventricular ejection fraction (RVEF) using MR predicts mortality in a group of patients with PAH and an improvement in RVEF at follow-up has been associated with better outcome independent of haemodynamic indices including pulmonary vascular resistance. This adds weight to the argument that direct visualisation of changes in the RV, may be more important than monitoring of invasive haemodynamics [11], this would seem logical given that it is RV failure that leads to death.

The current diagnostic paradigm for the diagnosis of PAH includes a clinical examination, six-minute walk test, multiple blood tests including BNP, lung function and radiological investigations [4]. The common radiological tests include: Chest X-ray, echocardiography, nuclear medicine perfusion scan, CT pulmonary angiography and in certain centres cardiac MRI. The purpose of this review is to showcase and explain the pathophysiologic stages of this disease and the use of various cardio-pulmonary vascular MR methods that can be used in daily practice to help diagnose, evaluate and follow up treatment response in this important group of patients. While “estimates” of systolic pulmonary artery pressure (sPAP) can be made from the velocity of the tricuspid regurgitation jet [12], the gold standard for clinical diagnosis of this disease remains direct measurement of pulmonary arterial pressure at RHC.

The clinical role of quantitative cardiac MR imaging methods in PAH

MRI has several inherent advantages including, high contrast resolution, no ionizing radiation and sequences with multiple aspects of sensitivity to cardiopulmonary form and functional changes. There are a range of pulse sequences utilised in a routine cardiopulmonary examination for suspected PH, detailed below, each with its own assets in the diagnostic and prognostic evaluation of patients with suspected PH. Imaging of

anatomical structure for structural assessment requires high spatial resolution whereas accurate imaging of cardiac function requires high temporal resolution and exploitation of the high sensitivity of MRI for assessment of wall motion and blood flow. The review of all of the imaging protocol allows for a comprehensive assessment of the heart and pulmonary vasculature in terms of form and function.

Biomarker assessment with imaging is very important. To establish a difference in treatment methodology drug companies rely on accurate and reproducible markers that detect changes with therapy [13, 14]. The precision of measurement means that fewer patients need to be imaged with MR versus the use of trans-thoracic echocardiography (TTE) [15]. For instance higher inter and intra observer agreement when using MR to measure the RV parameters of RV end diastolic volume (RVEDV) index, and tricuspid regurgitant volume [16] when compared with TTE [17, 18]. The cost savings of using a more precise and reproducible imaging method is significant and clinical practice is catching up with this fact.

Overview of cardio-pulmonary vascular MR methods for imaging PH

A standard protocol in the clinical assessment of patients with suspected PH based on current evidence includes a lung volume anatomical scan at breathhold for localizing, volumetric cardiac imaging for assessment of biventricular mass, volume and function, and stroke volume and cardiac output derived by phase contrast MRI are also performed at the pulmonary artery and aorta [19–22]. If the diagnosis of pulmonary thromboembolic disease is suspected, an MR angiogram of the pulmonary arteries and a time resolved contrast enhanced lung perfusion scan of should also be undertaken [19, 23], chronic pulmonary thromboembolism can be identified using these methods in patients with high sensitivity and specificity [19, 20, 24, 25]. The time resolved nature of the DCE perfusion angiography scan also allows for assessment of left-right heart shunts and co-lateral bronchial circulation. Finally, late gadolinium enhancement (LGE) imaging (following this contrast dose) is performed to assess for abnormal uptake of gadolinium that may suggest myocardial infarction or cardiomyopathy and to look for the presence of gadolinium accumulation at the RV interventricular septal insertion points [26–28].

The comprehensive cardio-pulmonary vascular MR imaging protocol

1. Localisers

Cardiac and lung morphology should first be scouted with breath-hold rapid imaging sequences. Short echo time balanced steady state free precession (bSSFP - True FISP, FIESTA, bFFE) imaging provides good signal from the parenchyma if the echo time is minimised to around 1 ms allowing lung pathology such as interstitial fibrosis which is related to PH in patients with pulmonary fibrosis and scleroderma to be assessed alongside CT [29]. The high signal to noise from the blood provides good contrast with the vessel lumen and thus serves as a non-contrast enhanced angiogram which can be useful in the delineation of adherent material in the central pulmonary arteries in CTEPH [19].

2. Black blood imaging

Cardiac gated black blood imaging is a technique that nulls the signal from flowing blood [30] using a cardiac gated dual inversion recovery fast spin echo sequence. Typical imaging parameters would be: $4-6 \times 8$ mm slices through the pulmonary arteries, spacing 2 mm, axial orientation, TI_1 50 ms, TI_2 551 ms, ETL 32, bandwidth 31.2 kHz, parallel imaging acceleration factor = 2, FOV 40 cm (36 cm FOV in phase direction), TE 42 ms, 256×256 matrix. The high spatial resolution images allow for the morphological assessment of boundaries between the lumen and vessel walls of cardiac chambers and vascular structures [31, 32]. Vessels with fast flowing blood appear black resulting in high contrast resolution between the vessel lumen and the vessel wall. Good suppression is achieved with fast blood flow such as in the aorta. However, it is less effective in the presence of turbulent or slow flowing blood such as that observed near vessel bifurcations [31] and in the pulmonary arteries particularly of patients with PH [33]. Frank et al studied the slow flow phenomenon in patients with PH and showed that in those patients with systolic pulmonary artery pressure >70 mmHg slow flow artifacts were observed [34]. Furthermore several groups have reported a correlation between the slow-flow phenomenon and systolic pulmonary artery pressure and pulmonary vascular resistance. In addition, an association between a qualitative score of the extent of slow-flow artifact and outcome has been identified, with the presence of artefacts within the proximal pulmonary main pulmonary arteries predicting mortality in a cohort of patients with PH (Figure 1) [35].

3. Cine cardiac MRI

Biventricular volume, function and mass—Focusing first on the beating heart, which can be captured with cine MR imaging by gating the acquisition to the cardiac cycle. One significant advantage over echocardiography is that the plane of imaging can be positioned in an accurate and reproducible fashion. bSSFP imaging is again the sequence of choice for cine cardiac MR imaging [36]. This technique utilises a high flip angle with short repetition time (TR) delivering high temporal resolution [17, 37]. The key difference of bSSFP over simple gradient echo imaging is that gradient waveforms are balanced and as such the refocused magnetisation between RF pulses results in improved blood-myocardial contrast resolution with a T2/T1 weighting, signal to noise and temporal resolution (Figure 2). Typical parameters are as follows: TR/TE 3.7/1.6 ms, 20 frames per cardiac cycle, slice thickness 8 mm, FOV 48, matrix 256×256 , band width 125 KHz/pixel.). A stack of images in the short axis plane with slice thickness of 8 mm (2 mm inter-slice gap) or 10 mm (0 mm interslice gap) are typically acquired fully covering both ventricles from base to apex. bSSFP cine imaging is usually performed with retrospective gating but when imaging patients with arrhythmia prospective gating may be beneficial.

Accurate and reproducible biventricular volume, function and mass measurements can be derived from cine bSSFP imaging [17, 38–40] and such measurements can provide useful clues in the clinical assessment of patients with suspected PH. [14, 41–43]. bSSFP cine imaging is usually performed with retrospective gating but when imaging patients with arrhythmia prospective gating may be beneficial. Volumetric imaging of the ventricles for quantification is typically performed in the short axis plane. There are difficulties with this approach, in particular determining the anatomy at the most basal slice is challenging. The

most common approach is to use the smallest chamber size as end-systole and largest as end-diastole. From end-systolic and end-diastolic images, measurements such as end diastolic volume (EDV), end systolic volume (ESV), ejection fraction (EF), stroke volume (SV) and mass can be calculated for both ventricles [14, 17, 38, 41, 44]. In addition, the pericardium [45, 46], interventricular septal position/motion [47], valve disease and regurgitant fractions [48–50], cardiomyopathy [51, 52], congenital heart disease [49, 50] and cardiac mass lesions [53] can be evaluated. Identification of end-systole can be difficult in patients with PH due to dysynchrony of LV and RV contraction [54, 55]. In patients with PH the RV contraction is prolonged with respect to the left, this accounts for lengthening (and a louder) second heart sound (P_2) in these individuals. Bowing of the inter-ventricular septum towards the left ventricle at the end of right ventricular systole is obvious in a short axis view and is indicative of the pressure differential between the right and left ventricles and results in a diminished RVEF [56].

Measurement of RV mass is similarly challenging, typically RV mass measurements include trabeculations and the papillary muscles [14] [55]. The interventricular septum is not considered part of the RV in mass analysis; however, trabeculations that project into the RV from the inter-ventricular septum are included in the analysis. It has been shown that a manual approach to RV analysis offers higher accuracy and reduced interobserver variability than a semi-automated segmentation method [14, 39]. Another practical challenge is that right and left ventricular volumes and function vary with age, gender and body surface area (BSA) [21, 57, 58]. Correction for all three variables may be important to identify small yet clinically significant cardiac volumetric abnormalities in an individual patient. Despite the challenges, cardiac MR volume and functional measurements are increasingly recognised as important in the clinical assessment of patients with PH, having the sensitivity to evaluate change at follow-up examinations [59] and identify treatment failure [41, 60]. Further development and validation of the methodologies is warranted to promote wider dissemination.

Inter-ventricular septum and left ventricular eccentricity—Elevated RV pressure causes the inter-ventricular septum to bow to the left in patients with PH [47, 61], this leftward motion of the interventricular septum causes the deformation of the LV, “D shape”, as a result of the pressure differential between LV and RV chambers (Figure 3). Beyar et al [62] demonstrated that interventricular septal bowing is present in an animal model when the pressure differential (RV pressure – LV pressure) exceeds 5 mmHg and a strong association between inter-ventricular septal curvature and the RV-LV pressure gradient was demonstrated as RV pressure increases. Previous studies using MRI have attempted to quantify paradoxical inter-ventricular septal position by measuring the curvature of the septum and have shown strong correlations with the severity of PH [47, 63].

Roeleveld et al, found a strong correlation between the radius of curvature of the inter-ventricular septal position at the point of maximal septal deviation with pulmonary artery systolic pressure [47]. Also, Dellegrottaglie et al, demonstrated in a similar fashion that in patients with PH or suspected of having PH, septal curvature derived from cardiac MR is comparable with RHC measurements and is an accurate metric for estimation of RV systolic pressure [64]. As the disease progresses, the RV dominates the interaction between the

cardiac chambers, resulting in a change of LV contour. To quantify this resultant LV deformation echocardiographic indices such as the LV systolic and diastolic eccentricity indices (sEI, dEI) [65] can be computed from the MRI. The sEI correlates with mPAP in patients with PH and its routine measurement using echocardiography has been recommended for the identification of RV dysfunction in patients with suspected PH [66]. Raymond et al [67] studied the prognostic importance of echocardiographic indices in patients with PAH, dEI was identified as a potential prognostic indicator, predicting mortality from Kaplan Meier log rank analysis, though it is noted that dEI was of marginal statistical significance ($p=0.074$) at Cox proportional hazards regression analysis. Thus, from these studies of septal curvature and LV eccentricity in patients with PH, it is clear that the configuration of the inter-ventricular septum and its effect on the LV are important measurements in the noninvasive hemodynamic assessment of the severity of PH.

4. Phase contrast MRI

Cardiac output and flow profile—Moving from the RV to the main pulmonary artery, blood flow can be measured with phase contrast imaging with gradient echo imaging with velocity encoding gradients [49, 68, 69]. Haemodynamic measurements such as forward flow, retrograde flow, average velocity and peak velocity can be determined. Cardiac output has been shown in several studies as an independent marker of adverse outcome in patients with PAH [5, 68, 70, 71]. Several MRI methodologies are well suited for the evaluation of cardiac output and stroke volume. MR volumetry can accurately and reproducibly evaluate the change in volume of the RV and LV chambers in healthy and diseased states [44, 72, 73] and phase contrast imaging is a robust technique for the evaluation of pulmonary arterial and aortic blood flow [69, 74–77]. Phase contrast MRI derived flow measurements have been shown to correlate with invasive measurements of pressure and resistance, for instance pulmonary artery pressure is negatively correlated with average velocity of blood flow in the main PA [77] and PVR can be estimated by calculating the ratio of the maximal change in flow rate during ejection by the acceleration volume [78]. Moreover, a recent study has identified that early retrograde flow in the pulmonary trunk is a characteristic feature in patients with PH [79]. Measurements are typically acquired in clinical practice in the pulmonary artery with a 2D gated cine sequence with velocity encoding in 3 dimensions. Phase contrast imaging parameters are as follows: TR 5.6ms, TE 2.7ms, FOV 48×28.8, slice thickness 10mm, bandwidth 62.5kHz, matrix = 256×128, 20 reconstructed cardiac phases. Typically velocity encoding values for flow sensitization in the PA in PH patient is 150cm/s.

Pulmonary artery stiffness and pulsatility—Pulsatile blood flow is produced from RV contraction driving blood through the main pulmonary artery towards the capillary bed. In patients with PH, increased pulmonary vascular resistance is associated with increased vascular stiffness [80], dilatation of the pulmonary arteries [81] and reduced flow velocity [82–84]. This impacts the RV-pulmonary artery coupled system with elevated RV workload resulting in RV remodeling with hypertrophy and dilatation eventually resulting in RV failure and death [40, 44, 85–87]. Pulmonary artery stiffness has been assessed in previous studies of patients with PH [80, 88, 89]. Typically the same bSSFP cine sequences as used for myocardial motion would be used. In a study of 134 patients with PH [90] and found a moderate relationship between pulmonary artery stiffness, as measured both by area change

(AC) and relative area change (RAC) of the pulmonary trunk (during the cardiac cycle), and pulmonary vascular resistance (Figure 4). RAC was correlated with adverse outcomes (p value < 0.05), and may be sensitive to mild PH given that compliance and resistance have an inverse-linear relationship and small increases in pulmonary vascular resistance are associated with larger proportional reductions in compliance [90]. Reduced RAC measured at the main pulmonary artery and the right main pulmonary artery have been shown to predict mortality in patients with PAH [91]. This mirrors the physiology found in the systemic circulation where reduced pulsatility of the aorta (stiffening of the wall and an increase in the pulse wave velocity) is independently linked to cardiovascular events and all-cause mortality.

5. Late Gadolinium Enhancement

Late gadolinium enhancement (LGE) imaging is a technique whereby T1-weighted inversion recovery gradient echo images are acquired approximately 10 to 15 minutes following intravenous (IV) injection of gadolinium based contrast agents (GBCA's). Typical pulse sequence parameters are as follows: TR 7.7ms, TE 3.6ms, slice thickness 8mm, FOV 45×40.5, matrix 256×224. A selective 180° inversion-recovery triggered to end-diastole was acquired in the short axis. The inversion time can be optimised by measuring the non-contrast enhanced myocardial T1 with a modified Look-Locker sequence [92]. Abnormal myocardium is permeable to contrast effectively delaying washout of the contrast from surrounding interstitium, scar, or dead myocytes. These damaged myocardial tissues represent in effect a different cellular compartment for which the transit times are distinct from the blood pool and the normally enhancing myocardium. Pathologies such as infarction or fibrosis where there is abnormal myocardial architecture increase the local concentration of contrast agent causing shorter T1 relaxation time compared to normal myocardium, this phenomenon is referred to as late or "delayed" enhancement [93, 94]. In the left heart, LGE imaging was developed primarily for assessment of scarring after myocardial infarction, with areas of scarring or fibrosis appearing as areas of high signal intensity. However this feature is not specific to myocardial infarction. Other cardiovascular disorders in which fibrosis is present can be detected with this method, for example hypertrophic cardiomyopathy, myocarditis, amyloid infiltration and PH [95]. LGE has been noted at the insertion points of the inter-ventricular septum in patients with PH (Figure 5) and the amount of late enhancement has been shown to be related to RV volume, mass and inter-ventricular septal position [96]. It is postulated that the degree of LGE relates to mechanical strain caused by elevated RV pressure and structural deformation at the insertion points [96]. Thus, LGE in PH is thought to represent pooling of contrast agent within an area of myocardium whose architecture has been affected by mechanical stress and hypertrophy. In a report of one case, the LGE was found to be related to contrast pooling at the septal insertion points, where myocardial disarray (not fibrosis) of the interdigitating fibers of the right and left ventricles was found. A recent study has shown that the presence of LGE on the myocardium of patients with PH is of prognostic value [26], with patient with LGE having worse outcome. However further research is required to establish the independent prognostic value of LGE as a predictor over clinical, RV and haemodynamic indices.

6. MR Angiography

Contrast enhanced MR angiograms can provide an overview of vessel pruning in IPAH and the delineation of thromboembolic material in CTEPH. Distinct angiogram patterns are evident in the PH subgroup types (see Figure 6) with characteristic dilated arteries with distal vessel pruning in IPAH and the pattern of splayed vessels evident in PH associated with chronic obstructive pulmonary disease/emphysema. Images can be acquired with single breath-hold short TE (~1ms) 3D spoiled gradient echo sequences with moderate parallel imaging (R 2 in both phase directions) in breath-holds of less than 12s. The dose and molarity of contrast agent needed for pulmonary MRA [97] and will depend upon the pulse sequence timing and flip angle. The use 10 ml of Gadovist® (Schering Gd-BT-D3OA) at an injection rate of 5ml/s followed by a 10 ml saline flush will provide good delineation of the pulmonary vessels and bolus timing can be synchronised with central k-space acquisition to bias the arterial or venous phase intensity. Just as in CTA, MRA is used in the setting of the acute onset of dyspnoea for the determination of pulmonary embolism, similar findings in the right heart can be seen.

These include the following: (a) an increase in the short axis of the RV when compared with the left ventricle (RV/LV diameter); (b) hepatic venous reflux on bolus phase; (c) azygous reflux on the bolus phase; (c) IVC distension; (d) determination of degree of obstruction using the Qanadli index; (e) pulmonary infarction; (f) pleural effusion. Also MRA has the ability to see perfusion defects on the bolus phase. The absolute amount of pulmonary perfusion may become an important prognostic tool in the future, as there are some early reports on using this simple metric from Dual energy CT. [98] wherein the obstruction index and RV/LV diameter was found to be highly correlated with the percentage of non-perfused lung.

7. Time resolved contrast enhanced angiography and pulmonary perfusion MR

Dynamic contrast enhanced (DCE) imaging allows for visualisation and measurement of the dynamic passage of a contrast bolus through the heart and lungs. For a typical MRI protocol 0.05–0.1 mmol/kg of gadolinium contrast agent (around 4 times weaker dose than for a MRA) is injected intravenously at 2–4ml/s, followed by a saline flush of 10ml. Continuous imaging immediately after contrast injection allows for a time resolved analysis of the transit of the contrast bolus through the cardiopulmonary system (Figure 7) [99–101]. Typically, T1-weighted gradient echo imaging is the sequence of choice with rapid data acquisition and the use of parallel imaging acceleration (acceleration factor of 2–4 times) allows the MR perfusion acquisition to be acquired within a single breath hold (10–20 seconds) with between 10–30 time resolved images. Recent advances in parallel imaging and MR sampling strategies have improved the spatial-temporal resolution of dynamic MRI. For example, interleaved variable density (IVD) sampling [102] combined with parallel imaging acceleration in 2 dimensions allow a single breath-hold (~23 sec) acquisition to achieve full chest coverage with sufficient (4.0 mm isotropic) spatial resolution and very high temporal frame rate (1.0 sec/frame) [103]. The acquired data can be reconstructed using either conventional view-sharing methods [104] or more sophisticated constrained reconstruction methods [102]. These show improved temporal fidelity without blurring at locations where

contrast dynamics change rapidly, such as the start of contrast arrival and the peak arterial phase.

While the assessment of bolus protocol and injection rate have been studied [105], the choice of contrast agent and their respective influence on DCE imaging in the lung have not been less well studied. It should be stated however, that unlike Iodine based contrast material and CTA perfusion imaging absolute quantification of lung perfusion is problematic as the concentration of contrast agent and T1 shortening on which the signal intensity is measured do not scale in a linear fashion. In other words, the signal intensity of a voxel is not directly correlated to concentration of contrast and in the pulmonary artery for example, there is limited mixing of contrast agent and the concentration can be quite high leading to saturation or “clipping” of the measured signal that underestimates the concentration-time profile of the measured arterial input function (AIF). One solution is to inject with a lower dose of contrast, but lower concentrations of contrast reduce signal to noise ratio (SNR) and sensitivity to perfusion defects in the lung parenchymal tissues [101]. One compelling alternative approach is the so-called “dual bolus” method used by Rise [106] to overcome the issue of non-linearity in the calculation of the AIF and improve SNR in the lung parenchyma. However, variations on the dual bolus method remain an area of active research.

The simplest means of analysis of DCE pulmonary perfusion is qualitative inspection of the peak signal enhancement images from the time series, which give a regional picture of pulmonary perfusion heterogeneity. The pre contrast baseline images can be subtracted from the peak intensity image to give a qualitative perfusion image (see examples in Figure 6). MR perfusion images like these provide a high-resolution robust and non-ionising alternative to nuclear medicine perfusion scintigraphy and have been shown to be of an equal or greater sensitivity to perfusion scintigraphy in the screening of CTEPH [107]. The time resolved nature of DCE perfusion MRI allows further quantitative interpretation of regional blood flow, volume and contrast transit time and several studies have investigated the value of these quantitative parameters in the clinical environment [99, 100, 108–111]. The association of DCE-MR cardiopulmonary transit times with cardiac function has been investigated in patients with left heart disease [109, 110]. Cardio-pulmonary transit times are significantly prolonged in patients with LV failure, correlating directly with LV volume and inversely with LVEF [110]. Previous studies have assessed DCE-MR in patients with PH by measuring transit times at pulmonary arterial and lung regions of interest. Sergiacomi et al [100] studied DCE MR indices in patients with PH associated with combined pulmonary fibrosis and emphysema, by measuring the transit time of a contrast bolus using ROI's placed in the distal main pulmonary arteries demonstrating good correlations with pulmonary arterial pressure and resistance. More recently, Skrok et al [112] studied the relationship of DCE transit times versus RV function and invasive pulmonary hemodynamics, showing significant associations with pulmonary vascular resistance and right atrial pressure. It should be noted that such measurements may prove to be useful in the prognostic evaluation and follow-up of patients with PAH [112], with a recent study showing prognostic significance of pulmonary transit times in patients with PAH. Transit time measurements predicted mortality independent of age, gender and WHO functional class; however invasive haemodynamic indices cardiac output, pulmonary vascular

resistance and DCE measurements were not independent of one another suggesting that they are closely related [113].

Advanced imaging and modeling methods in development for imaging pulmonary vascular disease

The following methods have recently been trialed in patients with PAH/PH. Pulse wave velocity can be calculated directly using the transit time technique by determining flow wave arrival time at two points in the proximal PAs using a high-temporal resolution flow mapping sequence and dividing the difference by the distance between them [114]. Pulse wave velocity indicates that there is not just transmission of flow but the velocity of propagation of the pulse along the vessel. This impact wave travels more quickly than the flow of blood within the vessel. With aging and stiffening of the vessel wall, loss of elasticity and compliance, the pulse wave velocity increases. With the loss of compliance the normal “windkessel effect” of energy storage by the compliant proximal pulmonary arteries is lost, decreasing efficiency of energy storage and reducing stroke volume in the face of high pressure defined by the pulmonary vascular resistance [115]. Thus, a high pulse wave velocity is an indication of worsened vessel compliance and increased ventricular work that is exacerbated by increased stress and oxygen demand.

A recent study assessing 4D flow patterns along the axis of the pulmonary artery showed vortex pulmonary flow in all patients with PH. Furthermore, the characteristics of the vortex including the relative period of existence of the vortex correlated well with pulmonary artery pressure [116]. Truong et al have very recently published some early results in the use of wall shear stress and compliance in the analysis of children with PAH. They show that 4D flow imaging with wall shear stress analysis of the right lower lobe pulmonary artery shows that children with PAH have lower wall shear stress than normals ($p < 0.018$). Also, as expected, the size of the main PA indexed to BSA was significantly larger in those children with PAH ($p < 0.003$) [117].

Despite the promising nature of these findings further validation of 4D flow MRI is required. Another emerging yet challenging MR methodology is cardiac MR spectroscopy, clinical ^{31}P -NMR spectroscopy has been applied to the left heart, but there is only scanty evidence of its use in the RV [118, 119], likely owing to technical challenges. Further technical development and assessing the feasibility of spectroscopy for the RV and the inter-ventricular hinge point, may be of value in the study of RV metabolism.

Non-Invasive Assessment of Hemodynamics with MRI

The ability to non-invasively and reliably estimate pulmonary arterial pressure is a key objective as this would permit the diagnosis of PH. Systolic pulmonary arterial pressure can be estimated with echocardiography using the tricuspid regurgitant jet velocity, the regurgitant jet is manually interrogated by the user at multiple angles [24] until the maximum velocity is achieved. This is more challenging with MRI as typically a single slice is prescribed with phase contrast imaging and due to motion of the valve during the cardiac cycle. Pulmonary arterial pressure has been estimated previously by measuring the effects of

PH on the heart using MRI. Initial results support the measurement of RV mass (RVMI) and ventricular mass index (VMI) [43]. For cardiac MRI to provide a complete hemodynamic assessment, in addition to right heart pressures, left sided cardiac pressure must be estimated in order to determine the trans-pulmonary gradient, a measurement that is necessary to derive pulmonary vascular resistance. In a recent study, mPAP has been accurately estimated using multivariate regression analysis of MRI indices, identifying VMI along with the angle of the interventricular septum as having additive value for the estimation of mPAP. Furthermore, using left atrial volume and phase contrast flow measurements as surrogates of left sided cardiac pressures and cardiac output pulmonary vascular resistance could be estimated showing the feasibility of MRI to estimate key pulmonary haemodynamic biomarkers [120]. Greater promise for estimating left sided heart pressure through the measurement of trans-mitral flow and myocardial tissue velocity has been shown, as performed with MRI may improve the reliability of the estimations [121]. Table 1 presents several methods of estimating pulmonary arterial pressure and pulmonary vascular resistance. Validation of current and development of new MR biomarkers [14, 24] encompasses, improving image acquisition and validation of image analysis methods that are crucial to further solidify the importance of MR as a robust, precise and reproducible tool for imaging assessment of the right heart in patients with PAH and other causes of PH. The combination of invasive pressure measurements and venous oxygen saturation and pulmonary capillary wedge pressure and pulmonary vascular resistance during MRI has been recently shown to be feasible in a porcine model of acute pulmonary embolism [122]. This ability to simultaneously measure these invasive clinical reference standards in patients during an MRI scan would be very useful and could eliminate entirely the need for a separate RHC.

MR imaging prognosis markers

Despite the continued development of effective treatment options, PAH remains an incurable disease with high morbidity and mortality [4, 71, 73, 123]. Established predictors of adverse outcome in PH include low cardiac output, elevated right atrial pressure, high pulmonary vascular resistance and reduced mixed venous oxygen saturations as measured at RHC [8–10, 70]. There is growing evidence for the role of MRI, as a reliable, reproducible and sensitive biomarker for patient follow-up in the context of risk stratification and the assessment of treatment response [11, 124]. Cardiac MR determined RV volume, stroke volume derived from phase contrast MRI, ejection fraction and LV volume independently predict mortality and treatment failure in IPAH [11, 125]. In addition, studies evaluating the prognostic value of pulmonary arterial stiffness in patients with pulmonary arterial hypertension (PAH) have shown that MR determined pulmonary arterial relative area change (RAC) predict mortality in PAH and in unselected patients with PH [90, 91, 126]. Table 2 Outlines the studies that have assessment MRI measurements in the prognostic evaluation of patients with PAH/PH

Future role of non-invasive imaging in the setting of pulmonary vascular disease

This review has illustrated the potential of MRI in the assessment of patients with suspected PH, with accuracy at least comparable to echocardiography. Furthermore, key haemodynamic measurements, of pressure, resistance and flow can be estimated using a non-invasive approach combining multiple MR indices [8]. Furthermore several studies have shown that directly visualizing and quantifying the changes in RV function with MRI at follow-up predict mortality independent of clinical and invasive haemodynamic measurements. These facts bode well for the future of MR in the initial workup and longitudinal follow-up of this group of diseases due to the fact that MR metrics of RV function and the associated morphometric indices are more precise and reproducible than TEE and also have less inter and intraobserver variability.

References

1. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009; 54(1 Suppl):S43–54. [PubMed: 19555858]
2. Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, Capener D, Sephton P, Hamilton N, Armstrong IJ, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. *Eur Respir J*. 2012; 39(4):945–955. [PubMed: 21885399]
3. Kiely DG, Elliot CA, Sabroe I, Condliffe R. Pulmonary hypertension: diagnosis and management. *BMJ*. 2013; 346:f2028. [PubMed: 23592451]
4. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2009; 30(20):2493–2537. [PubMed: 19713419]
5. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Annals of internal medicine*. 1991; 115(5):343–349. [PubMed: 1863023]
6. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *The New England journal of medicine*. 2004; 351(14):1425–1436. [PubMed: 15459304]
7. Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JS, Howard LS, Pepke-Zaba J, Sheares KK, Corris PA, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United kingdom and ireland. *Am J Respir Crit Care Med*. 2012; 186(8):790–796. [PubMed: 22798320]
8. Kane GC, Maradit-Kremers H, Slusser JP, Scott CG, Frantz RP, McGoon MD. Integration of clinical and hemodynamic parameters in the prediction of long-term survival in patients with pulmonary arterial hypertension. *Chest*. 2011; 139(6):1285–1293. [PubMed: 21071530]
9. Sandoval J, Bauerle O, Palomar A, Gomez A, Martinez-Guerra ML, Beltran M, Guerrero ML. Survival in primary pulmonary hypertension. Validation of a prognostic equation. *Circulation*. 1994; 89(4):1733–1744. [PubMed: 8149539]
10. Humbert M, Montani D, Souza R. Predicting survival in pulmonary arterial hypertension: time to combine markers. *Chest*. 2011; 139(6):1263–1264. [PubMed: 21652551]
11. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KM, Westerhof N, Vonk-Noordegraaf A. Progressive right ventricular dysfunction in

- patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol.* 2011; 58 (24):2511–2519. [PubMed: 22133851]
12. Hachulla E, Gressin V, Guillemin L, Carpentier P, Diot E, Sibilia J, Kahan A, Cabane J, Frances C, Launay D, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum.* 2005; 52(12):3792–3800. [PubMed: 16320330]
 13. Barbier CE, Johansson L, Lind L, Ahlstrom H, Bjerner T. Several sources of error in estimation of left ventricular mass with M-mode echocardiography in elderly subjects. *Uppsala journal of medical sciences.* 2011; 116(4):258–264. [PubMed: 22066974]
 14. Bradlow WMH, Keenan NG, Bucciarelli-Ducci C, Assomull R, Gibbs JS, Mohiaddin RH. Measuring the heart in pulmonary arterial hypertension (pah): Implications for trial study size. *Journal of magnetic resonance imaging: JMRI.* 2010; 31:117–124. [PubMed: 20027579]
 15. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson.* 2000; 2(4):271–278. [PubMed: 11545126]
 16. Hsiao A, Lustig M, Alley MT, Murphy MJ, Vasanawala SS. Evaluation of valvular insufficiency and shunts with parallel-imaging compressed-sensing 4D phase-contrast MR imaging with stereoscopic 3D velocity-fusion volume-rendered visualization. *Radiology.* 2012; 265(1):87–95. [PubMed: 22923717]
 17. Grothues FMJ, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *American heart journal.* 2004; 147:218–223. [PubMed: 14760316]
 18. Dragulescu A, Grosse-Wortmann L, Fackoury C, Mertens L. Echocardiographic assessment of right ventricular volumes: a comparison of different techniques in children after surgical repair of tetralogy of Fallot. *European heart journal cardiovascular Imaging.* 2012; 13(7):596–604. [PubMed: 22194094]
 19. Rajaram S, Swift AJ, Capener D, Telfer A, Davies C, Hill C, Condliffe R, Elliot C, Hurdman J, Kiely DG, et al. Diagnostic accuracy of contrast-enhanced MR angiography and unenhanced proton MR imaging compared with CT pulmonary angiography in chronic thromboembolic pulmonary hypertension. *European radiology.* 2012; 22(2):310–317. [PubMed: 21887483]
 20. Ley SKH, Heussel CP, Kramm T, Mayer E, Thelen M, Kreitner KF. Value of contrast-enhanced mr angiography and helical ct angiography in chronic thromboembolic pulmonary hypertension. *European radiology.* 2003; 13:2365–2371. [PubMed: 12712256]
 21. Maceira AMPS, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. *European heart journal.* 2006; 27:2879–2888. [PubMed: 17088316]
 22. Nikolaou KSS, Attenberger U, Scheidler J, Dietrich O, Kuehn B, Rosa F, Huber A, Leuchte H, Baumgartner R, Behr J, Reiser MF. Pulmonary arterial hypertension: Diagnosis with fast perfusion mr imaging and high-spatial-resolution mr angiography--preliminary experience. *Radiology.* 2005; 236:694–703. [PubMed: 15994997]
 23. Schiebler ML, Nagle SK, Francois CJ, Repplinger MD, Hamedani AG, Vigen KK, Yarlagaatta R, Grist TM, Reeder SB. Effectiveness of MR Angiography for the Primary Diagnosis of Acute Pulmonary Embolism: Clinical Outcomes at 3 Months and 1 Year. *Journal of magnetic resonance imaging: JMRI.* 2013 In Press. 10.1002/jmri.24057
 24. Bradlow WM, Gibbs JS, Mohiaddin RH. Cardiovascular magnetic resonance in pulmonary hypertension. *J Cardiovasc Magn Reson.* 2012; 14:6. [PubMed: 22257586]
 25. Rajaram S, Swift AJ, Telfer A, Hurdman J, Marshall H, Lorenz E, Capener D, Davies C, Hill C, Elliot C, et al. 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. *Thorax.* 2013; 68 (7):677–678. [PubMed: 23349220]
 26. Freed BHG-MM, Chandra S, Mor-Avi V, Rich S, Archer SL, Jamison EB Jr, Lang RM, Patel AR. Late gadolinium enhancement cardiovascular magnetic resonance predicts clinical worsening in patients with pulmonary hypertension. *Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance.* 2012; 14. [PubMed: 22300290]

27. Junqueira FPMR, Coutinho AC, Loureiro R, De Pontes PV, Domingues RC, Gasparetto EL. Myocardial delayed enhancement in patients with pulmonary hypertension and right ventricular failure: Evaluation by cardiac mri. *The British Journal of Radiology*. 2009; 82:821–826. [PubMed: 19398466]
28. Bradlow WMAR, Kilner PJ, Gibbs JS, Sheppard MN, Mohiaddin RH. Understanding late gadolinium enhancement in pulmonary hypertension. *Circulation Cardiovascular imaging*. 2010; 3:501–503. [PubMed: 20647584]
29. Rajaram S, Swift AJ, Capener D, Telfer A, Davies C, Hill C, Condliffe R, Elliot C, Hurdman J, Kiely DG, et al. Lung morphology assessment with balanced steady-state free precession MR imaging compared with CT. *Radiology*. 2012; 263(2):569–577. [PubMed: 22396606]
30. Song HK, Wright AC, Wolf RL, Wehrli FW. Multislice double inversion pulse sequence for efficient black-blood MRI. *Magn Reson Med*. 2002; 47(3):616–620. [PubMed: 11870851]
31. Yarnykh VL, Yuan C. Multislice double inversion-recovery black-blood imaging with simultaneous slice reinversion. *J Magn Reson Imaging*. 2003; 17(4):478–483. [PubMed: 12655588]
32. Edelman RR, Chien D, Kim D. Fast selective black blood MR imaging. *Radiology*. 1991; 181(3):655–660. [PubMed: 1947077]
33. von Schulthess GK, Fisher MR, Higgins CB. Pathologic blood flow in pulmonary vascular disease as shown by gated magnetic resonance imaging. *Ann Intern Med*. 1985; 103(3):317–323. [PubMed: 4026080]
34. Frank H, Globits S, Glogar D, Neuhold A, Kneussl M, Mlczoch J. Detection and quantification of pulmonary artery hypertension with MR imaging: results in 23 patients. *AJR Am J Roentgenol*. 1993; 161(1):27–31. [PubMed: 8517315]
35. Swift AJ, Rajaram S, Marshall H, Condliffe R, Capener D, Hill C, Davies C, Hurdman J, Elliot CA, Wild JM, et al. Black blood MRI has diagnostic and prognostic value in the assessment of patients with pulmonary hypertension. *Eur Radiol*. 2012; 22(3):695–702. [PubMed: 21993983]
36. Pohost GMHL, Doyle M. Clinical use of cardiovascular magnetic resonance. *Circulation*. 2003; 108:647–653. [PubMed: 12912794]
37. Grothues FSG, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *The American journal of cardiology*. 2002; 90:29–34. [PubMed: 12088775]
38. Hudsmith LEPS, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. *Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance*. 2005; 7:775–782. [PubMed: 16353438]
39. Pattynama PMLH, Van der Velde EA, Van der Geest RJ, Van der Wall EE, De Roos A. Reproducibility of mri-derived measurements of right ventricular volumes and myocardial mass. 1995; 13:53–63.
40. Saba TSFJ, Cockburn M, Cowan M, Peacock AJ. Ventricular mass index using magnetic resonance imaging accurately estimates pulmonary artery pressure. *European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology*. 2002; 20:1519–1524.
41. van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD, Postmus PE, Vonk-Noordegraaf A. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *European heart journal*. 2007; 28 (10): 1250–1257. [PubMed: 17242010]
42. Marcus JT, Gan CT, Zwanenburg JJ, Boonstra A, Allaart CP, Gotte MJ, Vonk-Noordegraaf A. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am Coll Cardiol*. 2008; 51(7):750–757. [PubMed: 18279740]
43. Swift AJ, Rajaram S, Condliffe R, Capener D, Hurdman J, Elliot CA, Wild JM, Kiely DG. Diagnostic accuracy of cardiovascular magnetic resonance imaging of right ventricular morphology and function in the assessment of suspected pulmonary hypertension results from the ASPIRE registry. *J Cardiovasc Magn Reson*. 2012; 14:40. [PubMed: 22720870]

44. Hagger DCR, Woodhouse N, Elliot CA, Armstrong IJ, Davies C, Hill C, Akil M, Wild JM, Kiely DG. Ventricular mass index correlates with pulmonary artery pressure and predicts survival in suspected systemic sclerosis-associated pulmonary arterial hypertension. *Rheumatology*. 2009; 48:1137–1142. [PubMed: 19605369]
45. Stark DDHC, Lanzer P, Lipton MJ, Schiller N, Crooks LE, Botvinick EB, Kaufman L. Magnetic resonance imaging of the pericardium: Normal and pathologic findings. *Radiology*. 1984; 150:469–474. [PubMed: 6691103]
46. Olson MCPH, McDonald V, Wisniewski R, Moncada R. Computed tomography and magnetic resonance imaging of the pericardium. *Radiographics: a review publication of the Radiological Society of North America, Inc.* 1989; 9:633–649.
47. Roeleveld RJMJ, Faes TJ, Gan TJ, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Interventricular septal configuration at mr imaging and pulmonary arterial pressure in pulmonary hypertension. *Radiology*. 2005; 234:710–717. [PubMed: 15634939]
48. Masci PGDS, Bogaert J. Valvular heart disease: What does cardiovascular mri add? *European radiology*. 2008; 18:197–208. [PubMed: 17762934]
49. Rebergen, SAvdWE.; Doornbos, J.; de Roos, A. Magnetic resonance measurement of velocity and flow: Technique, validation, and cardiovascular applications. *American heart journal*. 1993; 126:1439–1456. [PubMed: 8249802]
50. Markl M, Kilner PJ, Ebbers T. Comprehensive 4D velocity mapping of the heart and great vessels by cardiovascular magnetic resonance. *Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance*. 2011; 13(7):1–22. [PubMed: 21208447]
51. Wu KC. Utility of cardiac mri in the diagnosis of hypertrophic cardiomyopathy. *Current cardiology reports*. 2006; 8:41. [PubMed: 16507234]
52. Vogel-Claussen JSTM, Newatia A, Boyce D, Pinheiro A, Abraham R, Abraham T, Bluemke DA. Cardiac mri evaluation of hypertrophic cardiomyopathy: Left ventricular outflow tract/aortic valve diameter ratio predicts severity of lvot obstruction. *Journal of magnetic resonance imaging: JMRI*. 2012; 36(3):598–603. [PubMed: 22549972]
53. Pflugfelder PWWG, Boughner DR. Detection of atrial myxoma by magnetic resonance imaging. *The American journal of cardiology*. 1985; 55:242–243. [PubMed: 3966392]
54. Vonk-Noordegraaf AMJ, Gan CT, Boonstra A, Postmus PE. Interventricular mechanical asynchrony due to right ventricular pressure overload in pulmonary hypertension plays an important role in impaired left ventricular filling. *Chest*. 2005; 128:628S–630S. [PubMed: 16373882]
55. Katz JWJ, Boxt LM, Barst RJ. Estimation of right ventricular mass in normal subjects and in patients with primary pulmonary hypertension by nuclear magnetic resonance imaging. 1993; 21:1475–1481.
56. Beyar R. Heart inefficiency in pulmonary hypertension: a double jeopardy. *J Am Coll Cardiol*. 2008; 51(7):758–759. [PubMed: 18279741]
57. Lorenz CHWE, Morgan VL, Klein SS, Graham TP Jr. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. *Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance*; . 1999; 1:7–21.
58. CHL. The range of normal values of cardiovascular structures in infants, children, and adolescents measured by magnetic resonance imaging. *Pediatric cardiology*. 2000:21.
59. Roeleveld RJV-NA, Marcus JT, Bronzwaer JG, Marques KM, Postmus PE, Boonstra A. Effects of epoprostenol on right ventricular hypertrophy and dilatation in pulmonary hypertension. *CHEST Journal*. 2004; 125:572–579.
60. Mauritz GJKT, Marcus JT, Bogaard HJ, van de Veerdonk M, Postmus PE, Boonstra A, Westerhof N, Vonk-Noordegraaf A. Progressive changes in right ventricular geometric shortening and long-term survival in pulmonary arterial hypertension. *Chest*. 2012; 141:935–943. [PubMed: 21960697]
61. Dong SJCA, MacGregor JH, Petrank YF, Bergman DW, Belenkie I, Smith ER, Tyberg JV, Beyar R. Regional left ventricular systolic function in relation to the cavity geometry in patients with

- chronic right ventricular pressure overload. A three-dimensional tagged magnetic resonance imaging study. *Circulation*. 1995; 91:2359–2370. [PubMed: 7729022]
62. Beyar RDS, Smith ER, Belenkie I, Tyberg JV. Ventricular interaction and septal deformation: A model compared with experimental data. *The American journal of physiology*. 1993; 265:H2044–2056. [PubMed: 8285243]
 63. Dellegrottaglie SSJ, Poon M, Viles-Gonzalez JF, Sulica R, Goyenechea M, Macaluso F, Fuster V, Rajagopalan S. Pulmonary hypertension: Accuracy of detection with left ventricular septal-to-free wall curvature ratio measured at cardiac mr. *Radiology*. 2007; 243:63–69. [PubMed: 17392248]
 64. Dellegrottaglie SSJ, Poon M, Viles-Gonzalez JF, Sulica R, Goyenechea M, Macaluso F, Fuster V, Rajagopalan S. Pulmonary hypertension: Accuracy of detection with left ventricular septal-to-free wall curvature ratio measured at cardiac mr. *Radiology*. 2007; 243:63–69. [PubMed: 17392248]
 65. Ryan TPO, Dillon JC, Feigenbaum H, Conley MJ, Armstrong WF. An echocardiographic index for separation of right ventricular volume and pressure overload. *Journal of the American College of Cardiology*. 1985; 5:918–927. [PubMed: 3973294]
 66. Lopez-Candales ARN, Kochar M, Gulyasy B, Edelman K. Systolic eccentricity index identifies right ventricular dysfunction in pulmonary hypertension. *International journal of cardiology*. 2008; 129:424–426. [PubMed: 17692406]
 67. Raymond RJHA, Willis PW, Ralph D, Caldwell EJ, Williams W, Ettinger NA, Hill NS, Summer WR, de Boisblanc B, Schwartz T, Koch G, Clayton LM, Jobsis MM, Crow JW, Long W. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *Journal of the American College of Cardiology*. 2002; 39:1214–1219.
 68. Gatehouse PD, Keegan J, Crowe LA, Masood S, Mohiaddin RH, Kreitner KF, Firmin DN. Applications of phase-contrast flow and velocity imaging in cardiovascular MRI. *Eur Radiol*. 2005; 15(10):2172–2184. [PubMed: 16003509]
 69. Lotz J, Meier C, Leppert A, Galanski M. Cardiovascular flow measurement with phase-contrast MR imaging: basic facts and implementation. *Radiographics*. 2002; 22(3):651–671. [PubMed: 12006694]
 70. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation*. 2010; 122(2):156–163. [PubMed: 20585011]
 71. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, Rainisio M, Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *Journal of the American College of Cardiology*. 2002; 40(4):780–788. [PubMed: 12204511]
 72. McLaughlin VV, Davis M, Cornwell W. Pulmonary arterial hypertension. Current problems in cardiology. 2011; 36(12):461–517. [PubMed: 22035608]
 73. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation*. 2002; 106(12):1477–1482. [PubMed: 12234951]
 74. Mooij CF, de Wit CJ, Graham DA, Powell AJ, Geva T. Reproducibility of MRI measurements of right ventricular size and function in patients with normal and dilated ventricles. *Journal of magnetic resonance imaging: JMRI*. 2008; 28(1):67–73. [PubMed: 18581357]
 75. Kondo C, Caputo GR, Semelka R, Foster E, Shimakawa A, Higgins CB. Right and left ventricular stroke volume measurements with velocity-encoded cine MR imaging: in vitro and in vivo validation. *AJR Am J Roentgenol*. 1991; 157(1):9–16. [PubMed: 2048544]
 76. Ley S, Mereles D, Puderbach M, Gruenig E, Schock H, Eichinger M, Ley-Zaporozhan J, Fink C, Kauczor HU. Value of MR phase-contrast flow measurements for functional assessment of pulmonary arterial hypertension. *European radiology*. 2007; 17(7):1892–1897. [PubMed: 17225131]
 77. Sanz J, Kuschner P, Rius T, Salguero R, Sulica R, Einstein AJ, Dellegrottaglie S, Fuster V, Rajagopalan S, Poon M. Pulmonary arterial hypertension: noninvasive detection with phase-contrast MR imaging. *Radiology*. 2007; 243(1):70–79. [PubMed: 17329691]

78. Mousseaux E, Tasu JP, Jolivet O, Simonneau G, Bittoun J, Gaux JC. Pulmonary arterial resistance: noninvasive measurement with indexes of pulmonary flow estimated at velocity-encoded MR imaging--preliminary experience. *Radiology*. 1999; 212(3):896–902. [PubMed: 10478263]
79. Helderma F, Mauritz GJ, Andringa KE, Vonk-Noordegraaf A, Marcus JT. Early onset of retrograde flow in the main pulmonary artery is a characteristic of pulmonary arterial hypertension. *J Magn Reson Imaging*. 2011; 33(6):1362–1368. [PubMed: 21591004]
80. Sanz J, Kariisa M, Dellegrottaglie S, Prat-Gonzalez S, Garcia MJ, Fuster V, Rajagopalan S. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. *JACC Cardiovascular imaging*. 2009; 2(3):286–295. [PubMed: 19356573]
81. Devaraj A, Wells AU, Meister MG, Corte TJ, Wort SJ, Hansell DM. Detection of pulmonary hypertension with multidetector CT and echocardiography alone and in combination. *Radiology*. 2010; 254(2):609–616. [PubMed: 20093532]
82. Sanz J, Dellegrottaglie S, Kariisa M, Sulica R, Poon M, O'Donnell TP, Mehta D, Fuster V, Rajagopalan S. Prevalence and correlates of septal delayed contrast enhancement in patients with pulmonary hypertension. *The American journal of cardiology*. 2007; 100(4):731–735. [PubMed: 17697838]
83. Kondo C, Caputo GR, Masui T, Foster E, O'Sullivan M, Stulbarg MS, Golden J, Catterjee K, Higgins CB. Pulmonary hypertension: pulmonary flow quantification and flow profile analysis with velocity-encoded cine MR imaging. *Radiology*. 1992; 183(3):751–758. [PubMed: 1584932]
84. Nogami M, Ohno Y, Koyama H, Kono A, Takenaka D, Kataoka T, Kawai H, Kawamitsu H, Onishi Y, Matsumoto K, et al. Utility of phase contrast MR imaging for assessment of pulmonary flow and pressure estimation in patients with pulmonary hypertension: comparison with right heart catheterization and echocardiography. *Journal of magnetic resonance imaging: JMIR*. 2009; 30(5): 973–980. [PubMed: 19856412]
85. Marrone G, Mamone G, Luca A, Vitulo P, Bertani A, Pilato M, Gridelli B. The role of 1.5T cardiac MRI in the diagnosis, prognosis and management of pulmonary arterial hypertension. *The international journal of cardiovascular imaging*. 2010; 26(6):665–681. [PubMed: 20336377]
86. Benza R, Biederman R, Murali S, Gupta H. Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. *Journal of the American College of Cardiology*. 2008; 52(21):1683–1692.
87. Alunni JP, Degano B, Arnaud C, Tetu L, Blot-Souletie N, Didier A, Otal P, Rousseau H, Chabbert V. Cardiac MRI in pulmonary artery hypertension: correlations between morphological and functional parameters and invasive measurements. *European radiology*. 2010; 20(5):1149–1159. [PubMed: 20094890]
88. Jardim C, Rochitte CE, Humbert M, Rubinfeld G, Jasinowodolinski D, Carvalho CR, Souza R. Pulmonary artery distensibility in pulmonary arterial hypertension: an MRI pilot study. *The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology*. 2007; 29(3):476–481.
89. Revel MP, Faivre JB, Remy-Jardin M, Delannoy-Deken V, Duhamel A, Remy J. Pulmonary hypertension: ECG-gated 64-section CT angiographic evaluation of new functional parameters as diagnostic criteria. *Radiology*. 2009; 250(2):558–566. [PubMed: 19188324]
90. Swift AJ, Rajaram S, Condliffe R, Capener D, Hurdman J, Elliot C, Kiely DG, Wild JM. Pulmonary artery relative area change detects mild elevations in pulmonary vascular resistance and predicts adverse outcome in pulmonary hypertension. *Investigative radiology*. 2012; 47 (10): 571–577. [PubMed: 22914228]
91. Gan CT, Lankhaar JW, Westerhof N, Marcus JT, Becker A, Twisk JW, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. *Chest*. 2007; 132(6):1906–1912. [PubMed: 17989161]
92. Messroghli DR, Walters K, Plein S, Sparrow P, Friedrich MG, Ridgway JP, Sivananthan MU. Myocardial T1 mapping: application to patients with acute and chronic myocardial infarction. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2007; 58(1):34–40.
93. Bogaert JDS. Delayed contrast-enhanced mri: Use in myocardial viability assessment and other cardiac pathology. *European radiology*. 2005; 15 (Suppl 2):B52–58. [PubMed: 15801058]

94. Kim R, Fieno BS, Parrish TB, Harris K, Chen E-L, Simonetti, Bundy OJ, Finn JP, Klocke FJ, Judd RM. Relationship of MRI Delayed Contrast Enhancement to Irreversible Injury, Infarct Age, and Contractile Function. *Circulation*. 1999; 100:1992–2002. [PubMed: 10556226]
95. Teraoka K, Hirano M, Ookubo H, Sasaki K, Katsuyama H, Amino M, Abe Y, Yamashina A. Delayed contrast enhancement of MRI in hypertrophic cardiomyopathy. *Magn Reson Imaging*. 2004; 22 (2):155–161. [PubMed: 15010107]
96. Blyth KG, Groenning BA, Martin TN, Foster JE, Mark PB, Dargie HJ, Peacock AJ. Contrast enhanced-cardiovascular magnetic resonance imaging in patients with pulmonary hypertension. *European heart journal*. 2005; 26(19):1993–1999. [PubMed: 15899927]
97. Fink C, Puderbach M, Ley S, Plathow C, Bock M, Zuna I, Kauczor HU. Contrast-enhanced three-dimensional pulmonary perfusion magnetic resonance imaging: intraindividual comparison of 1.0 M gadobutrol and 0.5 M Gd-DTPA at three dose levels. *Invest Radiol*. 2004; 39(3):143–148. [PubMed: 15076006]
98. Chae EJ, Seo JB, Jang YM, Krauss B, Lee CW, Lee HJ, Song KS. Dual-energy CT for assessment of the severity of acute pulmonary embolism: pulmonary perfusion defect score compared with CT angiographic obstruction score and right ventricular/left ventricular diameter ratio. *AJR Am J Roentgenol*. 2010; 194(3):604–610. [PubMed: 20173135]
99. Ohno Y, Koyama H, Nogami M, Takenaka D, Matsumoto S, Onishi Y, Matsumoto K, Murase K, Sugimura K. Dynamic perfusion MRI: capability for evaluation of disease severity and progression of pulmonary arterial hypertension in patients with connective tissue disease. *Journal of magnetic resonance imaging: JMRI*. 2008; 28(4):887–899. [PubMed: 18821609]
100. Sergiacomi G, Bolacchi F, Cadioli M, Angeli ML, Fucci F, Crusco S, Rogliani P, Pezzuto G, Romeo F, Mariano E, et al. Combined pulmonary fibrosis and emphysema: 3D time-resolved MR angiographic evaluation of pulmonary arterial mean transit time and time to peak enhancement. *Radiology*. 2010; 254(2):601–608. [PubMed: 20093531]
101. Ohno Y, Hatabu H, Murase K, Higashino T, Nogami M, Yoshikawa T, Sugimura K. Primary pulmonary hypertension: 3D dynamic perfusion MRI for quantitative analysis of regional pulmonary perfusion. *AJR American journal of roentgenology*. 2007; 188(1):48–56. [PubMed: 17179345]
102. Wang K, Busse RF, Holmes JH, Beatty PJ, Brittain JH, Francois CJ, Reeder SB, Du J, Korosec FR. Interleaved variable density sampling with a constrained parallel imaging reconstruction for dynamic contrast-enhanced MR angiography. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 2011; 66(2):428–436.
103. Wang K, Schiebler ML, Francois CJ, Del Rio AM, Cornejo MD, Bell LC, Korosec FR, Brittain JH, Holmes JH, Nagle SK. Pulmonary perfusion MRI using interleaved variable density sampling and HighY constrained cartesian reconstruction (HYCR). *Journal of magnetic resonance imaging: JMRI*. 2013; 38(3):751–756. [PubMed: 23349079]
104. Riederer SJ, Tasciyan T, Farzaneh F, Lee JN, Wright RC, Herfkens RJ. MR fluoroscopy: technical feasibility. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 1988; 8(1):1–15.
105. Ohno Y, Murase K, Higashino T, Nogami M, Koyama H, Takenaka D, Kawamitsu H, Matsumoto S, Hatabu H, Sugimura K. Assessment of bolus injection protocol with appropriate concentration for quantitative assessment of pulmonary perfusion by dynamic contrast-enhanced MR imaging. *J Magn Reson Imaging*. 2007; 25(1):55–65. [PubMed: 17152051]
106. Risse F, Semmler W, Kauczor HU, Fink C. Dual-bolus approach to quantitative measurement of pulmonary perfusion by contrast-enhanced MRI. *Journal of magnetic resonance imaging: JMRI*. 2006; 24(6):1284–1290. [PubMed: 17051533]
107. Rajaram S, Swift AJ, Telfer A, Hurdman J, Marshall H, Lorenz E, Capener D, Davies C, Hill C, Elliot C, et al. 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE Registry. *Thorax*. 2013
108. Ley S, Mereles D, Risse F, Grunig E, Ley-Zaporozhan J, Tecer Z, Puderbach M, Fink C, Kauczor HU. Quantitative 3D pulmonary MR-perfusion in patients with pulmonary arterial hypertension:

- correlation with invasive pressure measurements. *European journal of radiology*. 2007; 61 (2): 251–255. [PubMed: 17045440]
109. Francois CJ, Shors SM, Bonow RO, Finn JP. Analysis of cardiopulmonary transit times at contrast material-enhanced MR imaging in patients with heart disease. *Radiology*. 2003; 227(2): 447–452. [PubMed: 12676971]
 110. Shors SM, Cotts WG, Pavlovic-Surjancev B, Francois CJ, Gheorghiade M, Finn JP. Heart failure: evaluation of cardiopulmonary transit times with time-resolved MR angiography. *Radiology*. 2003; 229(3):743–748. [PubMed: 14657311]
 111. Jeong HJ, Vakil P, Sheehan JJ, Shah SJ, Cuttica M, Carr JC, Carroll TJ, Davarpanah A. Time-resolved magnetic resonance angiography: evaluation of intrapulmonary circulation parameters in pulmonary arterial hypertension. *Journal of magnetic resonance imaging: JMRI*. 2011; 33(1): 225–231. [PubMed: 21182144]
 112. Skrok J, Shehata ML, Mathai S, Girgis RE, Zaiman A, Mudd JO, Boyce D, Lechtzin N, Lima JA, Bluemke DA, et al. Pulmonary arterial hypertension: MR imaging-derived first-pass bolus kinetic parameters are biomarkers for pulmonary hemodynamics, cardiac function, and ventricular remodeling. *Radiology*. 2012; 263(3):678–687. [PubMed: 22509050]
 113. Swift AJ, Telfer A, Rajaram S, Marshall H, Condliffe R, Capener D, Hurdman J, Elliot CA, Kiely DG, Wild JM. Dynamic contrast enhanced magnetic resonance imaging in patients with pulmonary hypertension. *Pulmonary circulation*. 2013
 114. Bradlow WM, Gatehouse PD, Hughes RL, O'Brien AB, Gibbs JS, Firmin DN, Mohiaddin RH. Assessing normal pulse wave velocity in the proximal pulmonary arteries using transit time: a feasibility, repeatability, and observer reproducibility study by cardiovascular magnetic resonance. *Journal of magnetic resonance imaging: JMRI*. 2007; 25(5):974–981. [PubMed: 17457797]
 115. Westerhof N, Lankhaar JW, Westerhof BE. The arterial Windkessel. *Medical & biological engineering & computing*. 2009; 47(2):131–141. [PubMed: 18543011]
 116. Reiter G, Reiter U, Kovacs G, Kainz B, Schmidt K, Maier R, Olschewski H, Rienmueller R. Magnetic resonance-derived 3-dimensional blood flow patterns in the main pulmonary artery as a marker of pulmonary hypertension and a measure of elevated mean pulmonary arterial pressure. *Circ Cardiovasc Imaging*. 2008; 1(1):23–30. [PubMed: 19808511]
 117. Truong U, Fonseca B, Dunning J, Burgett S, Lanning C, Ivy DD, Shandas R, Hunter K, Barker AJ. Wall shear stress measured by phase contrast cardiovascular magnetic resonance in children and adolescents with pulmonary arterial hypertension. *Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance*. 2013; 15(1): 81. [PubMed: 24034144]
 118. Spindler M, Schmidt M, Geier O, Sandstede J, Hahn D, Ertl G, Beer M. Functional and metabolic recovery of the right ventricle during Bosentan therapy in idiopathic pulmonary arterial hypertension. *J Cardiovasc Magn Reson*. 2005; 7(5):853–854. [PubMed: 16353449]
 119. Schwartz GG, Steinman SK, Weiner MW, Matson GB. In vivo ³¹P-NMR spectroscopy of right ventricle in pigs. *Am J Physiol*. 1992; 262(6 Pt 2):H1950–1954. [PubMed: 1621852]
 120. Swift AJ, Rajaram S, Hurdman J, Hill C, Davies C, Sproson TW, Morton AC, Capener D, Elliot C, Condliffe R, et al. Noninvasive Estimation of PA Pressure, Flow, and Resistance With CMR Imaging: Derivation and Prospective Validation Study From the ASPIRE Registry. *JACC Cardiovasc Imaging*. 2013
 121. Paelinck BP, de Roos A, Bax JJ, Bosmans JM, van Der Geest RJ, Dhondt D, Parizel PM, Vrints CJ, Lamb HJ. Feasibility of tissue magnetic resonance imaging: a pilot study in comparison with tissue Doppler imaging and invasive measurement. *J Am Coll Cardiol*. 2005; 45(7):1109–1116. [PubMed: 15808772]
 122. Garcia-Alvarez A, Fernandez-Friera L, Garcia-Ruiz JM, Nuno-Ayala M, Pereda D, Fernandez-Jimenez R, Guzman G, Sanchez-Quintana D, Alberich-Bayarri A, Pastor-Escuredo D, et al. Noninvasive Monitoring of Serial Changes in Pulmonary Vascular Resistance and Acute Vasodilator Testing using Cardiac Magnetic Resonance. *Journal of the American College of Cardiology*. 2013

123. Galie N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *European heart journal*. 2009; 30(4):394–403. [PubMed: 19155250]
124. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *Am Heart J*. 2004; 147(2):218–223. [PubMed: 14760316]
125. Marcus JTGC, Zwanenburg JJ, Boonstra A, Allaart CP, Gotte MJ, Vonk-Noordegraaf A. Left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *Journal of the American College of Cardiology*. 2008; 51:750–757. [PubMed: 18279740]
126. Mahapatra S, Nishimura RA, Oh JK, McGoon MD. The prognostic value of pulmonary vascular capacitance determined by Doppler echocardiography in patients with pulmonary arterial hypertension. *J Am Soc Echocardiogr*. 2006; 19(8):1045–1050. [PubMed: 16880101]
127. Moral S, Fernandez-Friera L, Stevens G, Guzman G, Garcia-Alvarez A, Nair A, Evangelista A, Fuster V, Garcia MJ, Sanz J. New index alpha improves detection of pulmonary hypertension in comparison with other cardiac magnetic resonance indices. *International journal of cardiology*. 2012; 161(1):25–30. [PubMed: 21596452]
128. Roeleveld RJ, Marcus JT, Boonstra A, Postmus PE, Marques KM, Bronzwaer JG, Vonk-Noordegraaf A. A comparison of noninvasive MRI-based methods of estimating pulmonary artery pressure in pulmonary hypertension. *J Magn Reson Imaging*. 2005; 22(1):67–72. [PubMed: 15971176]
129. Garcia-Alvarez A, Fernandez-Friera L, Mirelis JG, Sawit S, Nair A, Kallman J, Fuster V, Sanz J. Non-invasive estimation of pulmonary vascular resistance with cardiac magnetic resonance. *Eur Heart J*. 2011; 32(19):2438–2445. [PubMed: 21624902]
130. Hagger D, Condliffe R, Woodhouse N, Elliot CA, Armstrong IJ, Davies C, Hill C, Akil M, Wild JM, Kiely DG. Ventricular mass index correlates with pulmonary artery pressure and predicts survival in suspected systemic sclerosis-associated pulmonary arterial hypertension. *Rheumatology (Oxford)*. 2009; 48(9):1137–1142. [PubMed: 19605369]
131. Rajaram S, Swift AJ, Capener D, Elliot CA, Condliffe R, Davies C, Hill C, Hurdman J, Kidling R, Akil M, et al. Comparison of the diagnostic utility of cardiac magnetic resonance imaging, computed tomography, and echocardiography in assessment of suspected pulmonary arterial hypertension in patients with connective tissue disease. *J Rheumatol*. 2012; 39(6):1265–1274. [PubMed: 22589263]

Figure 1. Axial black blood images from a patient without PH (A) and a patient with PH (B), showing the absence and presence of pulmonary flow artefacts, respectively and enlargement of the main pulmonary artery in PH (B).

Figure 2. Short axis images from the systolic phase of the cardiac cycle in a patient with PAH. The inter-ventricular septum is flattened and there is marked RV dilatation and hypertrophy.

Figure 3. Systolic short axis MR images from a patient found to have normal pulmonary without PH (Image A) and a patient with PH (Image B) showing normal and abnormal) systolic septal configuration respectively.

Figure 4. Pulmonary artery images for calculation of relative area change Slices acquired orthogonal to the pulmonary artery, showing the pulmonary artery at its maximal (A) and minimal area (B). Relative area change and area change area calculated from these measurements.

Figure 5. Short axis late gadolinium enhancement (LGE) image of a patients with $mPAP < 25 \text{ mmHg}$ (right), patient with LGE at the right ventricular insertion points (left), this is a typical feature seen in most patients with PH.

Figure 6. Magnetic resonance angiograms (MRA) and perfusion images in three patients with PH: IPAH (1a/b), PH-COPD (2a/b) and a patient with CTEPH (3a/b)). 1a and 1b, shows vessel tortuosity and patchy perfusion in a patient with IPAH. 2a shows typical vessel splaying seen in patients with COPD/emphysema and associated reduced perfusion in the upper zones (2b). Figure 3a shows vessel stenoses and occlusions typical of a patient with CTEPH and the associated segmental perfusion defects are shown in 3b.

Figure 7.

Dynamic contrast enhanced images. Images show the passage of contrast through the cardiopulmonary system. Six frames are shown from the series of 48 time points. Time (t) is in seconds.

Table 1

Estimation of mPAP and PVR with MRI metrics in pulmonary hypertension

Author	#PH patients/# normals	Physiological metric	CMR metric	Cutoff Value for CMR metric	AUC	Correlation R ² or r value	P value
Moral [127]	152/33	mPAP	α	7.2	0.97	0.61 (R)	<0.001
Sanz [77]	42/17	mPAP	Average velocity	11.7	0.90	-0.73 (R)	<0.001
			Diastolic area	6.6	0.95	0.67 (R)	<0.001
		PVRI	Average velocity	11.7	0.92	-0.86 (R)	<0.001
Swift [120]	64+64*12+10 respectively		Diastolic area	6.0	0.93	0.64 (R)	<0.001
		mPAP	Model mPAP	32 mm Hg	0.96	0.67 (R ²)	<0.001
		PVR	Model PVR	3WU	0.94	0.76 (R ²)	<0.001
Roeleveld [128]	44	mPAP	VMI	Not studied	Not studied	0.56 (R)	<0.05
Garcia-Alvarez [129]	100 all PH 80 derivation 20 validation	PVR	Estimated PVR	4.2 WU	0.97	0.84 (R)	<0.001
Gan [91]	70/16	mPAP	RAC	Not studied	Not studied	0.47 (R) Exponential relationship	<0.05
Mousseaux [78]	19	PVR	maximal change in flow rate by the acceleration volume	Not studied	Not studied	0.90 (R)	<0.001
Swift [43]	194/39	mPAP	VMI	>0.4	0.91	0.78 (R)	<0.001
			LGE present/absent	Present	0.89	N/A	<0.001
			Diastolic PA area	>6cm ²	0.84	0.35 (R)	<0.05

Cardiovascular magnetic resonance (CMR) derived imaging metrics that are associated with elevated pulmonary arterial pressures (mPAP) or elevated pulmonary vascular resistance (PVR). Abbreviations: RHC- Right heart catheterisation, PAH- Pulmonary arterial hypertension, AUC- area under the curve receiver operator characteristic curve analysis of CMR metric, mPAP- mean pulmonary artery pressure, α - CMR derived metric that involves using the ratio between minimum PA area and RVEF (α =minimum PA area/RVEF), 64*- There is a separate validation cohort in this study from the initial cohort that helped to generate the regression equation for PVR and mPAP, RAC- relative area change of the pulmonary artery, WU- Woods units.

Table 2

MRI metrics prognostic of adverse outcomes in pulmonary hypertension.

Author	Length of Follow up/# patients and type of PH	CMR metric	Mean $\pm$ S.D or median value threshold for Kaplan Meier analysis*	Hazard Ratio*(confidence interval)	P value of univariate Metric
Van de Veerdonk [11]	1 year/110 PAH various	Baseline RVEF	36 $\pm$ 11%	0.938 (0.902–0.975)	0.001
		One year RVEF	–5% ($\pm$ 6%)	0.929 (0.875–0.985)	0.014
		RVESVI (ml/m ²)	47 $\pm$ 21 mL/m ²	1.014 (1.001–1.027)	0.048
		LVEDVI (ml/m ²)	42 $\pm$ 14 mL/m ²	0.962 (0.931–0.994)	0.019
		LVESVI (ml/m ²)	15 $\pm$ 9 mL/m ²	0.942 (0.888–0.998)	0.045
Van Wolferen [41]	1 year/64 IPAH	SVI (Phase contrast at pulmonary artery) (ml/m ²)	59 g/m ² *	0.32 (0.13–0.84)	0.019
		LVEDVI (ml/m ²)	25 mL/m ² *	0.31 (0.13–0.81)	0.016
		RVEDVI (ml/m ²)	40 mL/m ² *	4.2 (1.31–8.30).	0.011
Gan [91]	4 years/70	RAC (%) right main PA	16% *	0.87 (0.76–0.96)	<0.006
Swift [90]	20 months/134	RAC (%) main PA	8.1 $\pm$ 6.5% 10%	0.85 (0.74–0.98)	0.010
Hagger [130]	40 PAH-SSc	VMI	>0.56*	Log rank Not provided	0.017
Rajaram [131]		RVEDV VMI		1.02 (1.01–1.03) 5.56 (1.50–35.5)	0.0002 0.013
		RVIP-LGE	Present	10.0 (1.3 to 77.1)	0.026
Freed [26]	10 months/58				
Swift [113]	2 years/79	FWHM PTT	>8s >6.5s	1.08 (1.01 to 1.16) 1.10 (1.03 to 1.18)	0.034 0.010

Univariate CMR derived metrics prognostic of adverse outcomes in patients with pulmonary arterial hypertension or other causes of pulmonary hypertension from the literature. The hazard ratio (HR) represent change in the hazard for any increase of one unit in the candidate measurement. Abbreviations are as follows: mo- month, CMR- Cardiovascular Magnetic Resonance, RVEF- Right ventricular ejection fraction, LVEDVI (ml/m²) –Left ventricular end diastolic volume index, RVEDVI(ml/m²)– Right ventricular end diastolic volume index, RVESVI(ml/m²) Right ventricular end systolic volume index, t- values for those patients with right ventricular insertion point late gadolinium enhancement, SVI-Stroke volume index, One year RVEF- One year change in right ventricular ejection fraction, VMI ventricular mass index, RAC%- percent relative area change of the pulmonary artery between systole and diastole. RVIP-LGE –Right ventricular insertion point late gadolinium enhancement,