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SERIES "PULMONARY HYPERTENSION: BASIC CONCEPTS FOR PRACTICAL MANAGEMENT"
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Cardiac magnetic resonance imaging for the assessment of the heart and pulmonary circulation in pulmonary hypertension

L.E.R. McLure and A.J. Peacock

ABSTRACT: Pulmonary hypertension is a disease of the pulmonary arteries resulting in a progressive increase in pulmonary vascular resistance, ultimately leading to right ventricular failure and death. The functional capacity of the right ventricle is a major prognostic determinant. Our understanding of right ventricle performance in pulmonary hypertension has been hindered by the lack of techniques that give a reliable picture of right ventricle morphology and function. Cardiac magnetic resonance (CMR) imaging enables a unique combination of morphological and functional assessment of the right ventricle and pulmonary circulation. In this review article, we introduce the technique of CMR imaging, review its use in imaging of the heart and pulmonary circulation and discuss its current and future application to the management of patients with pulmonary hypertension.

There have been recent major advances in our understanding of the mechanism of disease development, in the diagnostic process, and in the treatment of pulmonary hypertension. Therapeutic advances in the management have reinforced the requirement for noninvasive, accurate and reproducible methods of assessment to act as ''end-points'' to measure the effects of treatment. We anticipate CMR imaging will increasingly be utilised as the primary modality for combined anatomic and functional assessments that enable more complete and efficient evaluation of pulmonary hypertension patients.

KEYWORDS: Cardiac magnetic resonance imaging, pulmonary circulation, pulmonary hypertension, right heart

In the present article, it is our aim to introduce the technique of cardiovascular magnetic resonance imaging, to review its use in imaging of the heart and pulmonary circulation and to discuss its current and future application to the management of patients with pulmonary hypertension. This paper is part of a series of articles published in the *European Respiratory Journal* summarising and commenting on the latest developments in pulmonary vascular disease (see footnote).

PULMONARY HYPERTENSION

Pulmonary hypertension is a disease of the pulmonary arteries that is characterised by vascular proliferation and remodelling [1, 2]. It results in a progressive increase in pulmonary vascular resistance (PVR) and ultimately, right ventricular failure and death. The diagnostic classification of pulmonary hypertension is described in table 1. This current classification was established during the 2003 World Symposium on Pulmonary Hypertension [3].

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TABLE 1 Diagnostic classification of pulmonary hypertension (Venice 2003)

Pulmonary arterial hypertension
Idiopathic
Familial
Associated with:
Connective tissue disease
Congenital systemic to pulmonary shunts
Portal hypertension
HIV infection
Drugs and toxins
Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders or splenectomy)
Associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease
Pulmonary capillary haemangiomatosis
Persistent pulmonary hypertension of the newborn
Pulmonary hypertension associated with left-sided heart disease
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Pulmonary hypertension associated with lung respiratory diseases or hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Pulmonary hypertension due to chronic thrombotic or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Nonthrombotic pulmonary embolism (tumour, parasites or foreign material)
Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour or fibrosing mediastinitis)

The functional capacity of the right ventricle is a major prognostic determinant in pulmonary hypertension. It is unknown why some patients with markedly elevated pulmonary artery pressure (P_{pa}) maintain well-preserved cardiac function for several years, while others with equal or less severe pulmonary hypertension suffer rapidly progressive right heart failure. One factor that has hindered the understanding of right ventricular performance in patients with pulmonary hypertension has been a lack of techniques that give a reliable picture of right ventricular morphological and functional change in the face of increasing outflow obstruction.

ASSESSMENT OF THE RIGHT VENTRICLE AND PULMONARY CIRCULATION

Anatomy of the right ventricle

The right ventricle is characterised by a crescent-like shape and a thin wall. The right ventricle pumps the same stroke volume as the left ventricle but with ~25% of the stroke work because of the low resistance of the pulmonary vasculature. Normally, the right ventricle has one-sixth of the muscle mass and performs against one-tenth of the vascular resistance compared to the left ventricle. Of note, longitudinal shortening is a greater contributor to right ventricular stroke volume than short-axis (circumferential) shortening [4]. In contrast to the symmetrical shape of the left ventricle, right ventricle geometry is complex. The normal right ventricle has an inflow component formed by the atrioventricular septum, tricuspid valve and subvalvular apparatus, an apical trabecular component and an outflow tract that continues into the pulmonary trunk. The right ventricular inflow and outflow regions are separated by the crista ventricularis and the right ventricle is ''wrapped around'' the left ventricle. This shape and orientation makes the evaluation of right ventricular volumes, systolic function and myocardial mass difficult using two-dimensional cross-sectional imaging modalities, such as echocardiography.

Assessment of the right ventricle

Several imaging modalities are available for the assessment of the right ventricle.

1) Echocardiography is the most well established imaging technique for screening and diagnosis of pulmonary hypertension [5]. As an imaging modality, it has the advantage of being widely available, inexpensive and safe. Echocardiography provides a quantitative estimate of systolic P_{pa}, using the peak velocity of the regurgitant jet through the tricuspid valve. It provides an assessment of associated anatomical abnormalities, *e.g.* evidence of congenital heart disease and right ventricle enlargement. This investigation relies upon geometric assumptions that can be difficult to adopt for the right ventricle, which has a complex shape. Limiting factors include

operator dependence and influence by prevailing conditions, such as heart rate and body habitus. Most studies report a high correlation (0.57–0.93) between echocardiography and right heart catheterisation (RHC) measurements of systolic P_{pa} [6], although ARCASOY *et al.* [7] concluded that estimation of systolic P_{pa} by echocardiography is frequently inaccurate in patients with advanced lung disease.

2) Radionuclide ventriculography can be used to image the right heart, although exposure to ionising radiation is a disadvantage. Attenuation artefacts are common, which makes it difficult to delineate the right atrium and right ventricle accurately.

3) Multi-slice computed tomography (CT) can assess all morphological features of right heart adaptation and failure in pulmonary hypertension. Modern contrast-enhanced CT studies permit delineation of the cardiac chambers, valves, great cardiac vessels and even the coronary artery lumen. Because data acquisition in spiral multi-detector CT is continuous, retrospective ECG gating allows for image reconstruction in any phase of the cardiac cycle. Thus, end-systolic and end-diastolic images can be produced to assess ventricular volumes and function. However, radiation exposure is a limitation and it is therefore doubtful that CT would be the modality of choice for assessment of the right heart, especially for follow-up examinations.

Assessment of the pulmonary circulation

The following imaging techniques are used for the assessment of the pulmonary circulation.

1) Ventilation/perfusion (V'/Q') lung scans may be entirely normal in some patients with PHT. Small peripheral nonsegmental defects in perfusion are often present, which are normally ventilated (V'/Q' mismatch). Lung V'/Q' scanning provides a means of diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH). Typically, the perfusion defects are found in lobar and segmental regions leading to segmental defects in the perfusion image, which are normally ventilated (unmatched V'/Q' defects). V'/Q' scanning showed a sensitivity of 90–100% with specificity of 94–100% for distinguishing between idiopathic pulmonary hypertension and CTEPH [8]. Exposure to ionising radiation is a disadvantage of this technique.

2) Contrast-enhanced spiral CT of the lungs is indicated in pulmonary hypertension patients when the V'/Q' scan is suggestive of segmental or subsegmental perfusion defects with normal ventilation. CT features of CTEPH include complete occlusion of pulmonary arteries, eccentric filling defects consistent with thrombi, recanalisation and stenoses or webs. Patients are exposed to ionising radiation and the risks of intravenous contrast agents during this investigation. Further limitations include the inability to perform dynamic images and flow measurements.

3) Traditional pulmonary angiography is required to identify patients with CTEPH who may benefit from pulmonary endarterectomy [8]. Pulmonary angiography is more accurate in the identification of distal obstructions. However, contrast angiography is an invasive procedure, with exposure to ionising radiation and contrast agents.

Right heart catheterisation

A diagnosis of pulmonary hypertension must be confirmed by RHC, which remains the gold standard for assessment of pulmonary haemodynamics. RHC provides direct and accurate measurements of P_{pa}, cardiac output and, hence, PVR. There are disadvantages to this procedure, but most important are the significant risks to the patient. A recent study by HOEPER *et al.* [9] assessed the risks associated with RHC (7,218 procedures) in patients with pulmonary hypertension. It was concluded that when performed in experienced centres, RHC in this patient group was associated with low morbidity and mortality rates (76 serious adverse events). Four fatal events were recorded in association with any of the catheter procedures, resulting in an overall procedure-related mortality of 0.055% (95% CI 0.01–0.099%). Apart from the risks, hospital admission is usually a procedure that may be inconvenient for patients. At present, RHC is required to confirm the diagnosis of pulmonary hypertension, to assess the severity of the haemodynamic impairment and to test the vasoreactivity of the pulmonary circulation. Some units also use RHC to determine success or response to treatment.

CARDIAC MAGNETIC RESONANCE IMAGING

Introduction

Cardiac magnetic resonance (CMR) imaging is well established in clinical practice for the diagnosis and management of a wide spectrum of cardiovascular disease. Its advancing role is related to technical improvements, which allow increasingly rapid and robust data acquisition. Use of CMR represents the specialised application of magnetic resonance to the cardiovascular system, employing specialised receiver coils, pulse sequences and gating methods. Images may be performed with ECG gating/triggering and with respiratory suppression (breath-holding or navigator gating), thereby reducing image artefacts.

CMR is fundamentally safe. No short- or long-term ill effects have been reported at current field strengths (<3 T). Magnetic resonance does not interfere with the electron shells involved in chemical binding (*e.g.* DNA) that can be altered by ionising radiation. The phenomenon of magnetic resonance is restricted to atomic nuclei with unpaired spin, *e.g.* hydrogen, carbon, oxygen, sodium, potassium and fluorine. The majority of clinical CMR imaging involves the hydrogen nucleus, which is abundant in water, fat and muscle.

Limitations of CMR

CMR is expensive, not widely available and requires significant operator expertise. It can be a difficult examination for pulmonary hypertension patients to complete owing to time duration and breath-holding requirements. Claustrophobia is a significant problem. This can be overcome in the majority of patients by using mild sedation, although this is often inappropriate in pulmonary hypertension patients. Ferromagnetic objects must not enter the magnetic resonance scanner area, because they will become projectiles. This is an extremely important safety issue. Common practice is to specifically check and verify that each medical device present in patients is magnetic resonance compatible. The radiofrequency field, which is used for excitation, can induce heating of tissue and implanted devices. It is possible to

stimulate sensitive tissues such as peripheral nerves owing to the rapidly changing gradient magnetic fields used to generate images. Myocardial stimulation has not been described with current hardware.

Ventricular morphology and function by CMR

Magnetic resonance imaging (MRI) produces tomographic still images that can accurately and reproducibly assess left ventricular and right ventricular chamber sizes, wall thickness and mass. The multifaceted nature of MRI enables it to be used not only for morphological assessment, but also for functional assessment. Conventional gradient-recalled echo or steady-state free-precession pulse (SSFP) sequences can be used to construct a cine image, which is a movie of 15–20 frames in which the full cardiac cycle can be seen; each movie frame represents 30–40 ms of the cycle. Recent technological advances enable the implementation of SSFP sequences which provide a substantially higher signal-to-noise ratio than can be obtained by conventional gradient–echo techniques. The contrast between myocardium and cavity blood [10] make planimetry of the interface accurate and easily reproducible for assessment of left and right ventricular function. The SSFP technique is the preferred CMR pulse sequence for acquisition of volumetric datasets of the left and right ventricles. Cine mode MRI allows regional and global systolic function to be evaluated because wall motion abnormalities can be identified. Ventricular volumes, ejection fraction and myocardial mass are usually obtained from a stack of contiguous ''bright blood'' cine CMR 5–10 mm slices covering the left and right ventricles acquired in short-axis or transverse orientation. Endocardial and epicardial contours are drawn during post-processing on end-diastolic and end-systolic frames, and left and right ventricular volumes are calculated as the sum of individual slice volumes (fig. 1). Ventricular mass is the product of myocardial volume and muscle-specific density (1.05 $g \cdot cm^{-3}$). A previous criticism of this technique has been the time required to analyse the cine data to generate accurate volume and mass data. New PC-based software solutions with intensity-based thresholding for semiautomated myocardial blood border definition has enabled analysis to become less time-consuming.

Impressive results for accuracy have been demonstrated by several investigators in various disease states [11–15]. The interstudy reproducibility of CMR-derived parameters of ventricular function and mass is good for both the left and right ventricles and is superior to two-dimensional and M-mode echocardiography [16–18]. The results from a study performed by GROTHUES *et al.* [19] demonstrate that the interstudy reproducibility of the right ventricle is lower than for the left ventricle, although CMR is still a reliable method and can be considered the gold standard for serial assessment of right ventricular volumes, function and mass.

Flow analysis

Phase contrast velocity mapping is an magnetic resonance sequence used to measure velocity and flow in blood vessels, or within the heart, in which each pixel in the image displays the signal phase, which is encoded. Volumetric flow (in millilitres per second) is obtained in each time frame by multiplying the spatial mean velocity (in centimetres per second) of blood flow with the cross-sectional area of the vessel

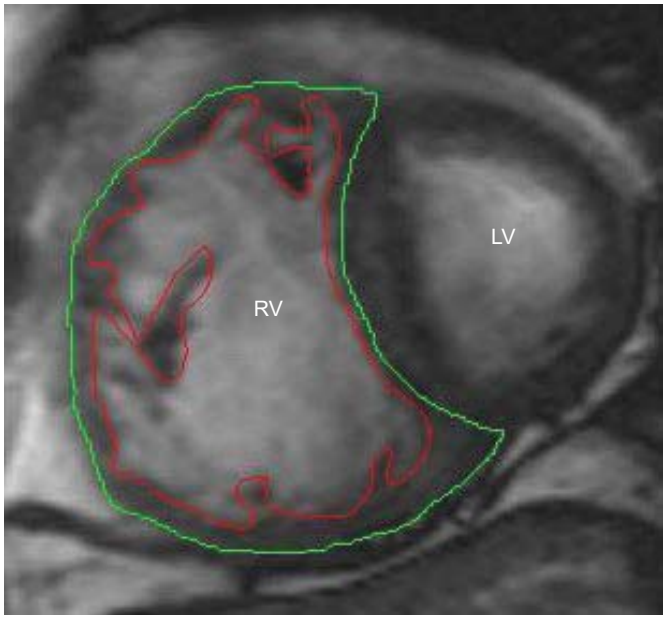

FIGURE 1. Planimetry of right ventricle (RV). Epicardial and endocardial borders of the right ventricular myocardium are manually traced at end-diastole on this short-axis cardiac magnetic resonance image. This scan is taken from a patient with idiopathic pulmonary hypertension. Right ventricular dilatation, hypertrophy and increased trabeculation are evident. LV: left ventricle.

(in square centimetres). Integrating the volumetric flow curve over systole gives the stroke volume. This imaging technique has been available for >20 yrs [20]. Velocity-encoded imaging has been shown to be a reliable method to measure blood flow in different vessels of the body. Analogous to Doppler echocardiography, this technique allows the calculation of stroke volume, cardiac output, ejection fraction, valvular regurgitant fractions and quantification of cardiac shunts, while mitral and tricuspid transvalvular flow profiles allow the assessment of ventricular diastolic filling patterns (E and A waves). Cardiac output and the pulmonary to systemic flow ratio measured with the use of this technique have been shown to be accurate [21, 22]. Stroke volume calculated from flow measurements in the pulmonary artery corresponds well with volumetric measurements of the right ventricle in healthy subjects. Phase contrast magnetic resonance flow is less accurate in patients with either cardiac arrhythmia during acquisition or turbulent blood flow; the presence of these is a general limitation of this technique. Of note, even when appropriate methods of acquisition have been used, there can be inaccuracies of flow measurement on some CMR systems caused by background phase errors due to eddy currents or uncorrected concomitant gradients.

Contrast-enhanced CMR imaging

Gadolinium is a contrast agent utilised in magnetic resonance scanning. It has seven unpaired electrons in its outer shell, and it hastens T1 relaxation, thereby increasing signal in the area of interest. Gadolinium alone is cytotoxic, but not if chelated with diethylenetriamine pentaacetic acid. It has similar pharmacokinetic properties to iodinated X-ray contrast but with minimal nephrotoxicity and anaphylaxis risk. Attention has been drawn, however, to recent reports identifying a possible link

between exposure to gadolinium-containing agents used in patients with end-stage renal disease and a rare, potentially life-threatening, condition referred to as nephrogenic systemic fibrosis. Regulatory authorities advise caution in the administration of gadolinium-containing agents in renally impaired patients.

In addition to evaluating the first-pass transit of gadolinium contrast, images can be obtained 10–15 min later, in a pseudoequilibrium phase. Gadolinium is avidly retained in abnormal myocardial regions, resulting in shortened T1 and increased signal intensity. The bright areas on the resulting images are described as areas of delayed contrast enhancement (DCE). DCE is not biologically specific and has been described in a variety of illnesses. Myocardial infarction, fibrosis and inflammation have all been shown to result in DCE using gadolinium as an *i.v.* contrast agent [23–27].

Magnetic resonance pulmonary circulation

Several methods have been proposed for MRI imaging of the pulmonary vasculature, both with and without the use of gadolinium. Three-dimensional gadolinium-enhanced magnetic resonance angiography (MRA) is now the most commonly applied. Contrast-enhanced MRA utilises three-dimensional ultrafast imaging sequences (T1 weighted) after *i.v.* injection of gadolinium and uses the first pass of this contrast agent [28]. Limitations of MRA include a lower spatial resolution and longer breath-hold when compared with CT.

Preliminary protocols are being developed to image lung perfusion into the diseased lung. These will allow for quantitative analysis of lung perfusion. This technique may allow for perfusion/functional assessment before and after disease targeted therapy.

CMR ASSESSMENT OF PULMONARY HYPERTENSION

It is becoming increasingly recognised that the right ventricle and the pulmonary vasculature should be approached, both diagnostically and therapeutically, as a unit in patients with pulmonary hypertension.

Cardiac morphology and function

Ventricular volumes

Right ventricular end-diastolic and end-systolic volumes are significantly elevated in pulmonary hypertension patients when compared with control subjects [11, 29–31]. These increased volumes represent the dilatation of the right ventricle (fig. 2). Right ventricular ejection fraction is significantly impaired in pulmonary hypertension compared with healthy subjects [29, 30, 32]. Right ventricular stroke volume [29] and right ventricular cardiac output are significantly reduced in patients with pulmonary hypertension compared with healthy control subjects [32]. A recent CMR study of 64 patients with idiopathic pulmonary arterial hypertension confirmed that a large right ventricular volume and a low stroke volume measured at baseline were strong independent predictors of mortality and treatment failure [33].

Using CMR imaging, left ventricular end-diastolic volume, left ventricular stroke volume and left ventricle peak filling rate (expressed as left ventricular end-diastolic volume per second) were significantly smaller in patients with pulmonary hypertension compared with healthy controls [29]. A reduced left ventricular end-diastolic volume at baseline predicts a poor outcome [33]. A CMR study by VONK NOORDEGRAAF *et al.* [32] compared patients with pulmonary hypertension secondary to emphysema and healthy controls. A significantly reduced left ventricular ejection fraction was demonstrated in the emphysematous patients and, especially, in those without right ventricular hypertrophy. Decreased left ventricular volumes can be explained by the increased PVR, which limits right ventricular stroke volume and, therefore, the volume available for left ventricle filling. Left ventricular septal bowing further reduces the left ventricular volume in early diastole, thus limiting the left ventricle filling process during the most important phase of rapid filling. GAN *et al.* [34] investigated the contribution of direct right to left ventricular interaction to left ventricle filling and stroke volume in pulmonary arterial hypertension patients and controls using CMR. They confirmed a close relationship between left ventricular end-diastolic volume and stroke volume, and concluded that ventricular interaction mediated by the interventricular septum (IVS) impairs left ventricle filling, contributing to a decreased stroke volume.

Ventricular mass

CMR has confirmed a significantly higher right ventricle mass in patients with pulmonary hypertension compared with healthy volunteers (fig. 2). Right ventricular hypertrophy is a consequence of the increased pulmonary afterload [13]. The left ventricular mass does not differ significantly from normal values in pulmonary hypertension patients [13]. A study by SABA *et al.* [35] of 26 patients who underwent CMR and echocardiography examination shortly after RHC showed that a ventricular mass index (VMI) >0.6 (obtained by dividing right ventricle mass by left ventricle mass) had a sensitivity of 84% and specificity of 71% for detecting pulmonary hypertension of various aetiologies. The VMI was more accurate than echocardiography in diagnosing pulmonary hypertension and demonstrated excellent correlation (r=0.81) with mean P_{pa} determined during right heart catheterisation [35]. This correlation was superior to that obtained from right ventricle mass alone. A recent, larger study by ROELEVELD *et al.* [36], however, showed a much weaker correlation between the VMI and mean P_{pa} (r=0.56), although the VMI was found to be the best among five different CMR-based methods for the estimation of mean P_{pa}.

Interventricular septal configuration

Cine CMR images show characteristic right ventricular wall motion changes in pulmonary hypertension patients. Distortion of the normal shape of the IVS has been reported in situations of right ventricular pressure and/or volume overload [37]. In the presence of increased systolic pressure in the right ventricle, the IVS flattens and may bow toward the left ventricle (fig. 2). Severe left ventricular septal bowing is often considered to be associated with an unfavourable prognosis in pulmonary hypertension [38]. Flattening and bowing of the septum can be expressed quantitatively as curvature, where the curvature is defined as the reciprocal of the radius. In 2005, ROELEVELD *et al.* [39] investigated whether a relationship existed between septum shape and systolic P_{pa} in patients with pulmonary hypertension. It was concluded that

systolic P_{pa} was proportional to septal curvature ($r=0.77$, $p<0.001$). Maximal distortion of the normal septal shape was found during the right ventricular relaxation phase. The cause of the leftward septum displacement appeared to be a pressure excess in the right ventricle relative to the left ventricle. Data obtained from 39 subjects showed a systolic P_{pa} >67 mmHg might be expected if left ventricular septal bowing is seen.

Right ventricular diastolic function

Diastolic function has been shown to be abnormal in diseases affecting the left ventricle. Often, diastolic dysfunction is an early sign of ventricular dysfunction and is currently being targeted therapeutically. GAN *et al.* [40] have shown that right ventricular diastolic dysfunction is present in pulmonary hypertension patients and can be relatively easily measured by CMR. Isovolumetric relaxation time (IVRT) may be a marker of right ventricular diastolic dysfunction and might predict burden of disease and clinical outcomes. IVRT correlates positively with both right ventricle mass and PVR, variables that are known to be of critical importance in the evaluation and prognosis of pulmonary hypertension [41]. Perhaps, more importantly, IVRT improves in response to standard therapies known to decrease right ventricular afterload, *e.g.* oral sildenafil [42]. These data suggest that MRI-measured right ventricular diastolic dysfunction and IVRT might be a good surrogate end-point for clinical trials on pulmonary hypertension. This comes at a very good time, where hard end-points, directly relevant to the right ventricle, need to be identified and used in pulmonary hypertension clinical trials; the validity of currently used primary end-points, such as the 6-min walk test (6MWT), are being challenged [43].

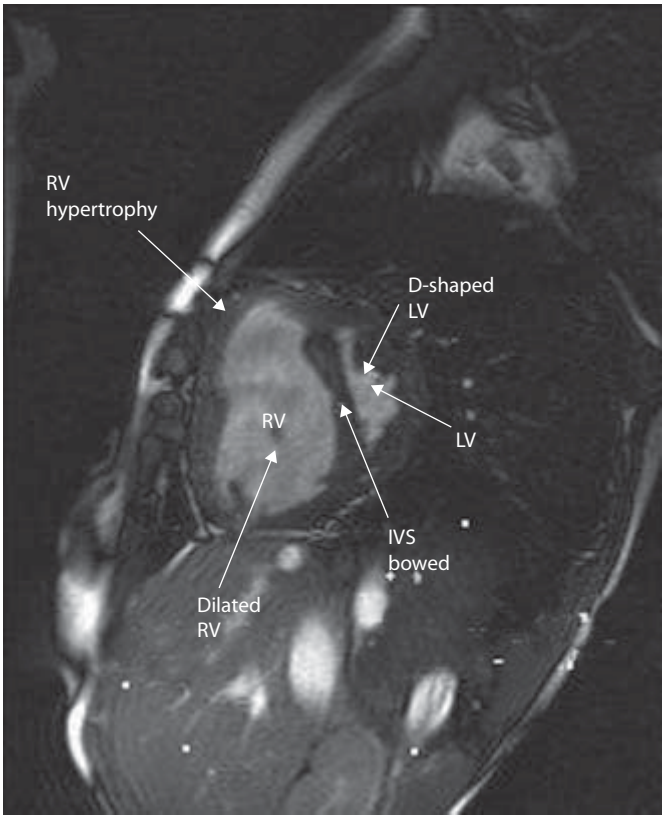

FIGURE 2. Cardiac magnetic resonance (CMR) short-axis image from a patient with pulmonary hypertension. A short-axis cine image at mid-ventricular level in early diastole. The CMR image was acquired from a patient with severe idiopathic pulmonary arterial hypertension. The right ventricle (RV) is grossly dilated and hypertrophied. The distorted interventricular septum (IVS) is bowed towards the left ventricle (LV; D-shaped) owing to right ventricular pressure overload.

Right ventricular contractility

Recent advances in magnetic resonance scanner hardware and software have enabled CMR guidance of endovascular catheters under real-time imaging (magnetic resonance fluoroscopy). This CMR approach is a promising tool for assessing right ventricular contractility in the clinical setting [44]. KUEHNE *et al.* [44] have demonstrated it is possible to combine CMR-guided invasive right ventricular pressure measurements with right ventricular volume values derived from cine CMR and to obtain right ventricular pressure–volume loops. This first study of six patients with early-stage idiopathic pulmonary arterial hypertension (mean±SD P_{pa} 57±21 mmHg) and six controls, demonstrated that the right ventricular and left ventricular stroke volumes and cardiac indices were significantly lower, despite higher right ventricular ejection fractions and right ventricular contractility in these patients. CMR-guided RHC was successfully used by the same group to assess the changes in PVR after nitric oxide inhalation in patients with idiopathic pulmonary arterial hypertension [45]. Reduction or elimination of X-ray radiation, added anatomic and functional information available with magnetic resonance, and the relative ease and accuracy of phase contrast magnetic resonance flow quantification may make this technique the method of choice for invasive measurement of PVR. This is a single-centre experience, and major limitations are cost and availability of magnetic resonance-compatible equipment. This procedure is not suitable for serial follow-up owing to its invasive nature.

Contrast-enhanced perfusion CMR

An interesting pattern of hyperenhancement within the right ventricle is described with delayed-contrast CMR in patients with pulmonary hypertension (fig. 3). This delayed-contrast enhancement pattern has a mid-wall distribution involving the right ventricle septal insertion points and the IVS [46]. A higher degree of enhancement was correlated with poorer right ventricular function and haemodynamics. When contrast enhancement was present in the IVS, it was associated with septal bowing on cine CMR. These data was confirmed by MCCANN *et al.* [27].

Stress CMR

Stress testing, by exercise or drug infusion, can be used to determine cardiac reserve. Physical exercise within the confines of the magnet is technically difficult and leads to image degradation. HOLVERDA *et al.* [47], however, demonstrated that idiopathic pulmonary arterial hypertension patients were unable to significantly increase stroke volume from rest to exercise, using an magnetic resonance-compatible ergometer. Pharmacological CMR stress can be used in patients with congenital heart disease to detect early right ventricular dysfunction. The physiological effects of exercise are imitated by a continuous infusion of a short-acting agent such as dobutamine (a relatively selective β_1-adrenoceptor

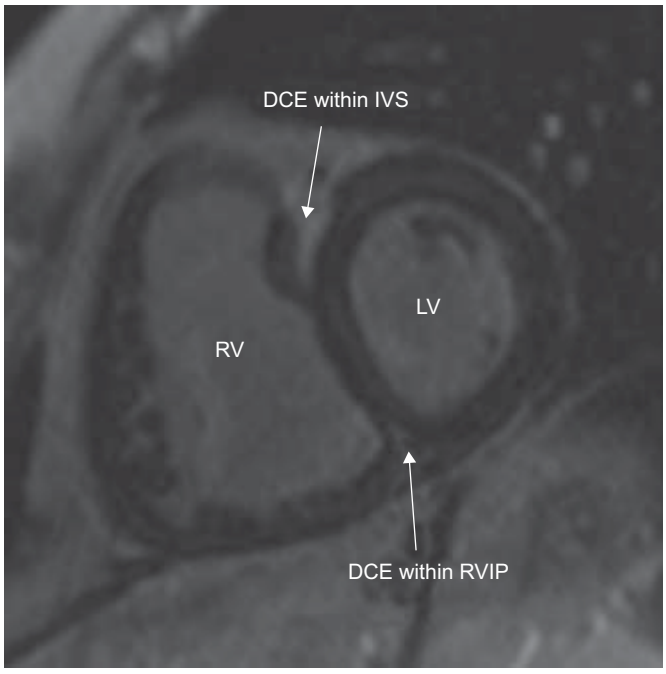

FIGURE 3. Delayed contrast-enhanced cardiac magnetic resonance (CMR) images of a patient with pulmonary hypertension. A contrast-enhanced short-axis CMR cine image was acquired at a basal ventricular level. The delayed-contrast enhancement (DCE) pattern has a mid-wall distribution involving the right ventricular insertion point (RVIP) and the interventricular septum (IVS). Trabeculations and papillary muscles are deliberately included in the analysis, as this has been shown to be a more accurate, although time-consuming, method. RV: right ventricle; LV: left ventricle.

agonist) [48]. Dobutamine has a positive inotropic effect on right ventricular contractility, which can be determined using MRI. To the best of our knowledge, there is no literature regarding pharmacological stress in pulmonary hypertension patients published at present.

Pulmonary circulation in pulmonary hypertension

CMR flow measurements

Velocity-encoded imaging is another CMR approach for the assessment of pulmonary hypertension. The analysis of these images enables the description of changes or irregularities of pulmonary blood flow in pulmonary hypertension. Previous studies using this technique have found highly inhomogeneous velocity profiles, a large volume of retrograde flow and decreased distensibility of the main pulmonary artery in patients with pulmonary hypertension [49, 50]. From the quantitative analysis of the pulmonary flow profile, noninvasive indices (*e.g.* acceleration time, defined as time from onset of flow to the peak velocity, and acceleration volume) have been derived for the assessment of PVR [51]. Peak blood flow velocity in the main pulmonary artery is lower in patients with pulmonary hypertension and shows inverse correlation with mean P_{pa} and PVR. When examined in patients with CTEPH, values after pulmonary endarterectomy were significantly higher than before surgical intervention, but did not reach normal range [52]. A significant reduction of peak velocity in both right and left pulmonary arteries was observed in patients with pulmonary hypertension secondary to cystic fibrosis [53]. As the study revealed no change in the flow of the main pulmonary artery, it was concluded that early and subtle changes of pulmonary haemodynamics are first noticeable in the periphery of the pulmonary arterial system. CMR could, therefore, be the method of choice for detection of early haemodynamic change before right ventricle function is altered.

In the setting of PHT, the most important applications of flow analysis include measurement of cardiac output and pulmonary to systemic flow measurements in the estimation of right-to-left and left-to-right shunts. Results from MRI flow measurements correspond well with thermodilution data obtained but cardiac output determination using velocity-encoded MRI offers advantages over the thermodilution method. It is noninvasive and the measurements depend less on changes in stroke volume from one cardiac cycle to another, because it averages over many cardiac cycles. In addition, the values are not influenced by tricuspid regurgitation to such a great extent.

Right ventricular stroke volume can be calculated as the difference between end-diastolic and end-systolic right ventricular volumes, or by the measurement of volumetric flow in the main pulmonary artery employing phase contrast velocity mapping. Stroke volume, calculated from flow measurements in the pulmonary artery and from volumetric measurements of the right ventricle, corresponds well in healthy controls, and show little divergence in patients with mild tricuspid regurgitation. However, with considerable tricuspid regurgitation (*e.g.* pulmonary hypertension patients), the volumetric stroke volume overestimates the actual stroke volume [29], because it is impossible to differentiate between the volume that moves back through the tricuspid valve and forward though the pulmonary valve. Flow measurement values are considered more reliable.

Distensibility of pulmonary artery

Pulmonary artery distensibility measured by CMR (expressed as per cent variation and calculated according to the following equation) was found to be significantly lower in pulmonary hypertension patients than it was in normal subjects (8% *versus* 23%) [49].

$$\text{Pulmonary artery distensibility} = ((\text{maximal area} - \text{minimal area})/\text{minimal area}) \times 100$$

A recent pilot, prospective study performed by JARDIM *et al.* [54] indicated that the noninvasive assessment of pulmonary artery distensibility by magnetic resonance reflected the acute response pattern in idiopathic pulmonary hypertension patients. Pulmonary artery distensibility was significantly higher in responders to an acute vasodilator test during invasive haemodynamic evaluation. GAN *et al.* [55] have recently demonstrated that proximal pulmonary artery stiffness (in terms of area distensibility and noninvasively assessed relative area change by CMR) predicted mortality in patients with pulmonary hypertension.

CMR pulmonary angiography

The typical findings of CTEPH (intraluminal webs and bands, vessel cut-offs, and organised thrombus) are well demonstrated by pulmonary MRA and can be seen in vessels to segmental level. Beyond the segmental level, the higher spatial resolution of conventional angiography makes it superior.

Surgical intervention is largely limited to proximal and segmental vessels, and in a study by KREITNER *et al.* [52], contrast-enhanced MRA correctly predicted surgical success in 33 out of 34 patients. The study demonstrated that three-dimensional contrast-enhanced MRA performed equally as well as X-ray pulmonary angiography for the visualisation of segmental pulmonary vessels (533 out of 533 segments), was slightly worse for subsegmental vessels (681 versus 733 segments), but was superior for the depiction of the central origin of thromboembolic material. Pulmonary MRA may be combined in the same examination with a variety of cine techniques to gauge cardiac function and flow. Contrast-enhanced MRA should identify patients with CTEPH that delineate typical findings and are potential candidates for surgery.

CMR pulmonary perfusion imaging

OHNO *et al.* [56] have demonstrated that three-dimensional dynamic contrast-enhanced MRI has the potential for assessment of disease severity in pulmonary hypertension patients. This technique showed significant differences in pulmonary blood flow and mean transit time between healthy and pulmonary hypertension subjects.

*P*PA ESTIMATION BY CMR

Repeated measurements of P_{pa} are sometimes used to assess disease progression in pulmonary hypertension. Echocardiography is safe and widely available but has limitations, as previously discussed [57]. MRI has been proposed to be an accurate alternative for echocardiography in estimating P_{pa}. Investigators have attempted to use CMR as a noninvasive means of estimating mean P_{pa} but none have reported any advantages over echocardiography. Several estimators based on different MRI techniques have been described in recent years, including acceleration time (the time of onset of forward flow to the moment of maximum flow velocity in the main pulmonary artery), acceleration time/ejection time ratio, pulse wave velocity, cross-sectional area of the main pulmonary artery and ventricular mass index. Right ventricular end-diastolic wall thickness has been shown to correlate well with mean P_{pa} in idiopathic pulmonary arterial hypertension and some cases of secondary pulmonary hypertension [58, 59]. A linear relationship between right ventricle mass and mean P_{pa} has been described for idiopathic pulmonary arterial hypertension [13]. The ratio of the main pulmonary artery diameter over descending aortic diameter has also been shown to correlate with mean P_{pa} in pulmonary hypertension. The VMI was found to be the best among five different CMR-based methods for the estimation of P_{pa} and similar to echocardiography ($r=0.55$ using the modified Bernoulli equation and peak tricuspid regurgitation velocity), but not accurate enough to replace RHC in clinical practice [36]. A computed method for the noninvasive magnetic resonance assessment of pulmonary hypertension has been elaborated, in which a combination of physical variables, including main pulmonary artery blood flow velocity at peak systole, maximal systolic main pulmonary artery cross sectional area and biophysical parameters including patient height, weight and heart rate were used to estimate P_{pa} [60, 61].

FOLLOW-UP OF PATIENTS WITH PULMONARY HYPERTENSION

CMR is increasingly used in patients with pulmonary hypertension for the evaluation of pathological and functional changes in the heart and pulmonary circulation. CMR provides a direct evaluation of right ventricular size, mass, morphology and function [62]. Normal ranges have been established [13, 50]. CMR findings in right ventricular failure include right ventricular dilatation, tricuspid regurgitation, right ventricular hypertrophy, interventricular septal flattening or paradoxical motion, and change in chamber morphology from a normal crescent shape to a more concentric form. Noninvasive assessments of blood flow (including stroke volume and cardiac output) and distensibility in the pulmonary arteries can be made [63–65]. There is good correlation between RHC and magnetic resonance, suggesting that magnetic resonance data could be used as a surrogate of right heart haemodynamics [64].

Pulmonary hypertension experts gathered in 2007 at the End Points Meeting held in Turnberry, UK. Physicians currently rely on the World Health Organization (WHO) functional class, 6MWT, biological markers (brain natriuretic peptide (BNP) levels), echocardiography and RHC to follow up patients with pulmonary hypertension. These investigations have acknowledged limitations. The question of which end-points are most relevant in the assessment of pulmonary hypertension has been the topic of intense discussion. The WHO functional class has been an important end-point in clinical trials of pulmonary hypertension, although the assignment of patients to categories is subject to the bias of investigators, which limits its usefulness as an end-point. The 6MWT is a submaximal exercise test which can be performed by patients who are incapable of tolerating maximal exercise testing [66]. The 6MWT has been used widely as a primary end-point in clinical trials, but flaws have been highlighted in its performance. The 6MWT must be performed correctly using the appropriate guidelines [66]. There are concerns that the 6-min walk distance (6MWD) is affected by a number of factors other than pulmonary hypertension including age, sex, height, weight and musculoskeletal conditioning [67]. Furthermore, it has been shown that the 6MWD can improve considerably with rehabilitation measures alone [43]. Echocardiography is the most well established and accessible imaging modality for follow-up of patients with pulmonary hypertension. Doppler echocardiography is suitable for serial assessments, although it has some limitations, as discussed previously in the present article. Serial measurement of plasma NT-proBNP (N-terminal-pro-BNP) has great attractions as an end-point. Its presence in the blood is related to right ventricular dysfunction, it is simple to measure and relatively inexpensive. Some remarkable relationships between plasma BNP/NT-proBNP and various elements of right ventricular dysfunction have been shown [46, 68, 69]. It would appear that BNP/NT-proBNP measurement is a dynamic measurement reflecting the current state of the right ventricle. An increase in NT-proBNP over time reflects right ventricular dilatation concomitant to hypertrophy and deterioration of systolic function [69]. We await the results of large-scale studies to determine the role of BNP in the assessment and management of patients with pulmonary hypertension. The normalisation of measures

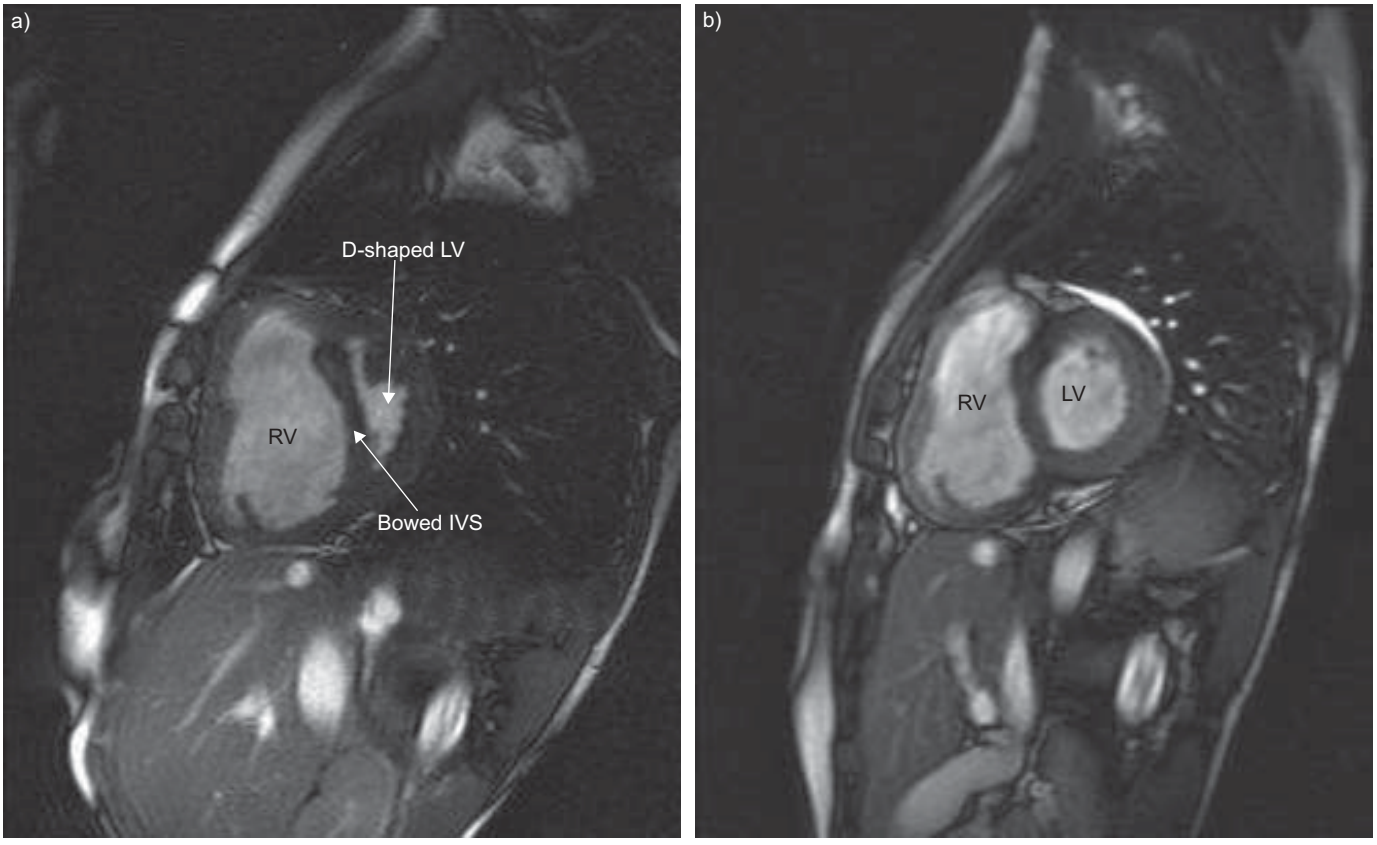

FIGURE 4. Pre- and post-treatment cardiac magnetic resonance (CMR) imaging. A 14-yr-old male presented with dyspnoea and exertional syncope. Idiopathic pulmonary arterial hypertension was diagnosed. a) Baseline short-axis mid-ventricular CMR image demonstrating a grossly dilated right ventricle (RV) with pronounced bowing of the interventricular septum (IVS) compromising the left ventricle (LV). Oral bosentan and anticoagulation therapy were commenced. There was considerable functional improvement. b) A CMR scan repeated at 6 months demonstrated a dramatic improvement in cardiac morphology.

of cardiovascular haemodynamics would be an ideal end-point. However, resting haemodynamics improve only marginally in most patients, even when their clinical response appears to be excellent [70], and do not reflect changes that may occur with exercise. Clinical improvement, therefore, is only partly related to a modification of resting haemodynamics in most patients. Furthermore, RHC is an invasive procedure that is not ideal for serial evaluation.

It has been suggested that characteristics for an ideal marker in pulmonary hypertension might include [71]: 1) it should be heart or lung specific; 2) it should be abnormal in pulmonary hypertension; 3) sample collection should be simple; 4) the marker should be easy to measure; 5) values should be reproducible; 6) values should follow the course of the disease (*i.e.* increasing if patients deteriorate and falling if patients improve); and 7) abnormal values should be indicative of a poor survival.

CMR imaging fulfils these stated characteristics. As discussed, modern CMR protocols provide us with abundant information regarding the ventricular myocardium and pulmonary vasculature. Right ventricular volumes, muscle mass and functional parameters, including stroke volume, ejection fraction and cardiac output, differ significantly in pulmonary hypertension compared to healthy subjects. CMR imaging is easily performed by trained MRI technicians/physicians and the majority of patients tolerate this noninvasive investigation well. Manual planimetry of the myocardium and flow analysis is simple to perform and reproducible although time-consuming at present. Sequential MRI is the optimal tool to monitor therapeutic effects on vascular remodelling and right heart performance. CMR-derived right ventricle functional parameters correlate well with established haemodynamic parameters of prognostic significance. Although RHC remains the definitive assessment of pulmonary hypertension at present, the noninvasive evaluation of cardiac morphology and function and of the pulmonary circulation is a new and promising application for CMR imaging.

CMR AS AN END-POINT

MRI is gaining a dominant role as the reference method for clinical trials assessing longitudinal changes in left ventricular function after therapeutic interventions [72–74]. The accuracy and reproducibility of CMR in assessing cardiac morphological and functional variables leads to low interstudy variability, which translates into a significant reduction in sample sizes required to test the efficacy of therapeutic interventions. It is expected that the number of clinical trials using CMR parameters as study end-points will increase considerably in the future. Ultimately, however, patient outcome is the relevant clinical issue. Future effort should be directed toward testing whether changes in cardiac variables as measured by magnetic

resonance indeed translate into differences in patient outcome. An example of CMR-measured improvement is seen in figure 4.

Deterioration of right ventricular function at follow-up examinations indicates an unfavourable prognosis because functional impairment of the right ventricle is the major factor in disease progression and decline in life expectancy [75]. VAN WOLFEREN *et al.* [33] performed a longitudinal CMR study which confirmed right ventricular dilatation and a decrease in stroke volume and left ventricular diastolic volume are strong predictors of treatment failure and death at follow-up. Medical therapies or surgical interventions may stop, or even reverse, this process, and the improvement of right ventricular function could be detected by MRI.

At present, there are few studies in pulmonary hypertension which have utilised CMR as an end-point so far. Changes in right ventricle mass, function and pulmonary artery blood flow have been demonstrated by CMR following lung transplantation in several studies [74, 76, 77]. In 2003, MICHELAKIS *et al.* [78] performed a small nonrandomised pilot study of five patients with pulmonary hypertension to investigate the effect of sildenafil 50 mg *t.i.d*. Right ventricle mass was utilised as an end-point. Sildenafil significantly reduced right ventricle mass and increased the right ventricular stroke volume as measured by CMR. The pathological septal shift towards the left ventricle was reversed by long-term sildenafil therapy. In a prospective study of pulmonary hypertension patients with prostacyclin therapy, the significant increase in right ventricular stroke volume (pulmonary arterial flow analysis) corresponded well with functional improvement (WHO functional class and 6MWT) [30]. The functional and morphological effects of pulmonary endarterectomy in patients with CTEPH was assessed by KREITNER *et al.* [52] using a combination of three-dimensional gadolinium contrast-enhanced MRA, cine CMR and velocity-encoded CMR. CMR demonstrated surgical success in 33 out of the 34 patients, with improvement of the initially depressed right ventricular ejection fraction, which correlated with the decrease in mean P_{pa} and disappearance of septal bowing in 68% of patients after surgery. In a comparison study between sildenafil and bosentan, right ventricle mass (measured by CMR) did not change after 3 months of bosentan treatment, whereas sildenafil reduced right ventricle mass [79]. It was demonstrated by CMR that the addition of sildenafil reversed right ventricular dilatation and hypertrophy in patients receiving treatment [80]. More recently, 16 patients with pulmonary arterial hypertension were assessed by CMR at baseline and after 12 months treatment with bosentan [81]. After treatment, cardiac index, PVR and 6MWT distance increased. There was a trend towards improvement in right ventricular stroke volume ($p=0.08$), although there was no change in right ventricular ejection fraction or right ventricular end-diastolic volume, as determined by CMR.

CONCLUSIONS

CMR imaging enables a unique combination of morphological and functional assessment of the right ventricle and pulmonary circulation. CMR has emerged over recent years as the gold standard for detailed study of the right ventricle and has become an established modality for the physiological assessment of pulmonary hypertension patients in cross-sectional studies, longitudinal follow-up studies and clinical trials of therapy. We anticipate that MRI will increasingly be utilised as the primary modality for combined anatomic and functional assessments that enable more complete and efficient evaluation of patients with pulmonary hypertension. CMR is currently being used as an end-point in the multinational European Union-funded Framework 6 EURO-MR project for pulmonary hypertension. We wait to see whether the promise of CMR as a successful end-point is fulfilled.

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