Therapeutic Strategies in PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) is a rare condition; yet this very rarity can be a disadvantage when it comes to treatment, making PAH difficult to diagnose, resulting in suboptimal patient care. Furthermore, the global burden of PAH remains poorly understood and largely underestimated, as PAH commonly presents as a comorbidity with such conditions as systemic sclerosis, COPD, idiopathic pulmonary fibrosis and left-heart dysfunction. However, in recent years there has been significant investment in developing new therapies for PAH, and treatment for this previously neglected disease is set to enter a new era.

This new work draws on the recent published literature and clinical trials to review the latest developments in our understanding of the disease, new advances in therapy and current opinion on best practice approaches to management. Internationally-recognised authorities on PAH provide expert analysis of these advances and critical commentary on the data presented to help explain the implications of these findings for future clinical practice.

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PULMONARY ARTERIAL HYPERTENSION

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Imaging of the right heart and pulmonary circulation

A. Vonk Noordegraaf, T. C. Konings, J. T. Marcus

INTRODUCTION

Imaging techniques play an important role in the diagnosis of pulmonary arterial hypertension (PAH). However, the role of imaging in the follow-up of patients with PAH has been limited until now, despite the fact that right ventricular (RV) failure is the primary cause of death in this disease. Reasons for this might be the technical difficulties encountered in accurately measuring RV structure and function, as well as a lack of studies confirming the clinical relevance of these techniques in assessing the effects of treatment and prognosis.

Echocardiography is a well-established and accessible imaging modality for the screening and diagnosis of pulmonary hypertension (PH). One limitation of this technique is that it is highly operator-dependent. In addition, volumetric measurements rely upon geometric assumptions that are difficult to apply to the complex shape of the right ventricle. Emerging techniques for an accurate assessment of RV structure and function are magnetic resonance imaging (MRI) and computed tomography (CT). Both of these techniques enable the imaging of the pulmonary vasculature and perfusion. This chapter provides an overview of the technical possibilities and limitations of these imaging modalities in the imaging of the right ventricle and pulmonary circulation.

ECHOCARDIOGRAPHY

In clinical practice, echocardiography is the mainstay of evaluation of RV structure and function, being easily accessible and versatile in comparison with other imaging modalities. However, echocardiography of the RV is challenging because of the multipartite, multiplanar morphology of the RV, its anterior position and the poor visualisation of the RV anterior free wall. In addition, its multiplanar geometry makes it difficult to use summation-type volume calculations.

Echocardiography can be used as a non-invasive screening tool in the field of PH and plays an important role in the diagnostic algorithm. It provides not only an estimate of PH at rest and during exercise, but can also help to exclude left-sided heart disease as a cause
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of PH, predict prognosis, monitor treatment effects and detect preclinical stages of the disease [1]. Knowing the characteristic echocardiographic features of the RV is important in both initial and serial evaluation of PH patients. Multiple echocardiographic techniques are available for the assessment of these characteristics.

**ONE- AND TWO-DIMENSIONAL IMAGING (M-MODE AND 2D)**

Right and left ventricular size and function, the morphology of cardiac valves, abnormal anatomical connections, atrial pathology and the presence of pericardial effusion are well established with 2D echocardiography (Figure 1.1).

Most patients with PH present with enlarged right-sided chambers, pulmonary artery (PA) dilatation, RV hypertrophy and reduced global RV systolic function due to chronic RV pressure overload [2]. This is accompanied by a systolic flattening of the interventricular septum (IVS) and an increased thickness with an abnormal IVS/posterior left ventricular wall ratio >1. Due to the displacement of the IVS to the left, the ventricle appears D-shaped with reduced systolic and diastolic volumes but preserved global systolic function. Interatrial right-to-left septum bowing might be another characteristic of PH. Pericardial effusion can be seen due to impaired venous and lymphatic drainage secondary to elevated right atrial pressure.

Assessing the RV volume, the simplest and most routinely used methods include linear dimensions and areas obtained from single tomographic echocardiographic planes. The best correlations between single-plane measurements and RV volumes have been obtained with the maximal short axis dimension and the planimetered RV area in the 4-chamber view. The area–length method, which uses an ellipsoidal or pyramidal model, correlates better with RV volume than the Simpson’s rule, using disk volumes.

In clinical practice, right ventricular ejection fraction (RVEF), the ratio of change in ventricular volume during the cardiac cycle, is the most commonly used index of RV contractility. Two-dimensional assessment of RVEF can be estimated with Simpson’s rule and the

![Figure 1.1. Transthoracic echocardiogram: parasternal short-axis view. Due to elevated pressures in the right ventricle (RV), the interventricular septum (IVS) is displaced, leading to a D-shaped left ventricle (LV) with reduced systolic and diastolic volume.](image-url)
area–length method, although the correlation with MRI and radionuclide-derived RVEF is modest [3].

Right ventricular fractional area change (RVFAC) represents the ratio of systolic area change to diastolic RV area, measured in the 4-chamber view. In end-stage pulmonary disease, a good correlation exists between RVFAC and RVEF [4].

A quantitative measurement of RV systolic performance is the tricuspid annual plane systolic excursion (TAPSE). This method reflects the longitudinal systolic excursion of the lateral tricuspid annulus towards the apex. It is measured with M-mode imaging in the apical 4-chamber view. A moderate correlation exists between TAPSE and radionuclide-derived RVEF [5].

(COLOR-) DOPPLER ECHOCARDIOGRAPHY

Colour-Doppler echocardiography can detect intracardiac shunts and regurgitation of cardiac valves. In 86% of cardiovascular patients, a tricuspid regurgitation (TR) of measurable quality can be detected. The development of TR in patients with PH is likely to be related to the presence of annular dilatation, altered RV geometry and the apical displacement of tricuspid leaflets [6]. Using the systolic regurgitant tricuspid flow ($v$), an estimation of the systolic pulmonary artery pressure (sPAP) can be made by Doppler echocardiography. In the absence of pulmonary outflow tract obstruction, sPAP is equivalent to the RV systolic pressure, which can be calculated with the simplified Bernoulli equation:

$$RVSP = 4v^2 + \text{right atrial pressure (RAP)}$$

$v$ is measured with a continuous wave Doppler signal and the RAP is an estimated value using characteristics of the inferior vena cava.

Peak early diastolic and end-diastolic velocities of pulmonary regurgitation correlate significantly with mean and diastolic PA pressure [7].

RV outflow tract acceleration time, defined as the interval from onset to the maximal velocity of forward flow in a pulsed wave Doppler derived signal, has a negative correlation with mean pulmonary artery pressure (mPAP). A RV outflow tract acceleration time <100 ms reflects an increased mPAP.

RV myocardial performance index (TEI index), which is the ratio of isovolumetric time intervals to ventricular ejection time, can be calculated from the pulsed wave Doppler derived inflow and outflow durations. This parameter has been described as a global non-geometric index of systolic and diastolic ventricular function. The normal value of this index is 0.28 ± 0.04 and this value increases in the presence of RV dysfunction [8].

Left ventricular diastolic filling is frequently abnormal in patients with PH. Doppler echocardiography can analyse this abnormal filling pattern by determining the ratio between the early diastolic peak transmural flow velocity (E) and the late diastolic peak velocity (A) [9] with a ratio E/A <1 being indicative for abnormal left ventricular diastolic filling. Reasons for this abnormal filling pattern in PH might be a reduced left atrial filling, abnormal left ventricular (LV) relaxation, the presence of abnormal LV geometry because of RV enlargement and leftwards septal displacement at the early diastolic phase, or possible myocardial oedema [10].

TISSUE DOPPLER IMAGING

Tissue Doppler imaging (TDI) has been introduced to estimate RV function by measuring the deformation and velocity of the RV structures during the cardiac cycle. The tissue velocity along a long axis in the 4-chamber view relates to longitudinal shortening and gives a one-dimensional view of unit velocity at predefined anatomical sites. Tissue Doppler imag-
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There are five major deflections visualised on TDI of the RV tricuspid annulus: the isovolumetric contraction wave, systolic velocity (Sa), isovolumetric relaxation wave, early diastolic velocity (Ea) and late diastolic velocity (Aa). A peak systolic tissue Doppler signal Sa <11.5 cm/s identifies the presence of ventricular systolic dysfunction (RVEF <50%) [11]. Moustapha and colleagues [12] have found that Sa and Ea were significantly lower in patients with PH compared to controls, indicating depressed RV function. Caso and coworkers [13] reported a prolonged myocardial relaxation time by TDI in patients with pulmonary disease and PH.

Tissue Doppler imaging may be useful in estimating the mean pulmonary capillary wedge pressure (PCWP). The early diastolic velocity of the mitral annulus corrected for the early diastolic mitral inflow velocity (E/Ea) relates well to the PCWP (E/Ea >15 = PCWP >20 mmHg) and may be used to estimate LV filling pressures [14, 15]. Low filling pressures in PH patients are indicative for a non-cardiac aetiology of PH [9].

The myocardial performance index can also be derived with TDI and more accurately compared to Doppler imaging. It has a higher frame rate and samples a discrete segment of the ventricular myocardium. The systolic and diastolic time intervals are measured in the same cardiac cycle, eliminating beat-to-beat variation.

Using conventional TDI, a non-functional segment being sampled can still possess adequate velocities by being tethered to a normally functional adjacent segment. Strain analysis, measuring deformation, and strain rate measuring velocity of deformation, can overcome this limitation. In various disease entities, tissue Doppler-derived strain is a sensitive index of segmental contractile function and correlates to invasive and magnetic resonance measures of RV [16]. Lopez-Candales and colleagues [17] found that PH patients had lower RV longitudinal free wall strain compared with healthy volunteers.

Although strain imaging has overcome the problem of segmental myocardial tethering, strain is still angle- and load-dependent. Speckle imaging and velocity vector imaging, two novel two-dimensional measures of myocardial motion, may overcome this problem and merit further investigation.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY (3D)

Three-dimensional echocardiography is a promising method for more accurate assessment of the RV volume and function. Although less limited by geometric assumptions when compared with 2D echocardiography, 3D echocardiography is still dependent on an adequate acoustic window and problems with delineation of the anterior wall and identification of the infundibular plane need to be overcome. These limitations might explain the inaccuracy of 3D echocardiography to measure RVEF [18].

EXERCISE ECHOCARDIOGRAPHY

Because of non-specific and subtle signs, particularly in its early stages, the detection of PH requires a high clinical index of suspicion. Along with clinical assessment, electrocardiogram (ECG), radiographic investigations and Doppler echocardiography, exercise echocardiography can be an excellent tool to screen patients for exercise-induced PH. However, the full physiological range of pulmonary pressure responses to exercise in relation to gender and age in athletes and non-athletes as a reference for cardiovascular evaluation and counselling still has to be defined. For example, in healthy people, moderate exercise leads to only a mild increase in sPAP in contrast to well-conditioned athletes who are capable of reaching sPAP levels of around 60 mmHg with exercise as a consequence of increased flow and left atrial pressure [1].
Another advantage of exercise echocardiography is the diagnosis of diastolic dysfunction, which does not manifest itself under resting conditions [19].

**PROGNOSTIC AND THERAPEUTIC IMPLICATIONS**

The prognosis of PH is relatively poor and related to the severity of RV dysfunction which can be evaluated by echocardiography. Together with a number of haemodynamic and non-invasive parameters, various echocardiographic indicators of right heart impairment, including indexed right atrial area, the degree of septal shift in diastole, a high RV myocardial performance index and the severity of pericardial effusion, have been associated with unfavourable outcomes [1].

Besides providing prognostic information, Doppler echocardiography can be a helpful tool in the assessment of the effect of medical interventions. Galie and colleagues [20] evaluated the effects of the oral endothelin receptor antagonist bosentan in comparison to placebo on echocardiographic and Doppler measures in a group of PAH patients. Their results showed that patients treated with bosentan showed less RV dilatation, increased LV dimensions, greater stroke volume and higher cardiac index compared to the placebo group. There was also an improvement in RV ejection, LV early diastolic filling and a beneficial effect on the diameter of the inferior vena cava and pericardial effusion. The treatment effect on 6-minute walking distance (6MWD) was 37 m in favour of bosentan. This study showed that echocardiography can be successful in detecting changes in cardiac structure and function associated with medical treatment and can be used to monitor the efficacy of new therapeutic interventions.

**MAGNETIC RESONANCE IMAGING**

Magnetic resonance imaging, although expensive and technically demanding to use accurately, is an emerging technique in the study of the right ventricle and pulmonary circulation. Technical MRI requirements for this type of imaging are a cardiac imaging package for acquiring ECG triggered cine images, and a flow package for measuring blood flow. In addition, a cardiac or body surface coil is required to obtain images with a sufficient signal-to-noise ratio. With regard to the magnetic field strength, any field strength above 0.5 Tesla will suffice. In addition, the physician needs access to post-processing software tools for quantification of volumes, flow and perfusion. For the patient, the MRI must be safe and thus any contraindications must be excluded (e.g. the presence of an infusion pump or cardiac pacemaker).

**ASSESSMENT OF RIGHT AND LEFT VENTRICULAR FUNCTION AND MASS BY MRI**

Right and left ventricular function assessment is reached by localizing the cardiac 4-chamber view in a standardised procedure [21], and by obtaining a contiguous stack of short-axis cine images of the RV and LV from which RV and LV mass, volume and function are derived. The patient is instructed to hold their breath in relaxed expiration during all image acquisitions, and also during ‘scout’ imaging for localisation of the heart. If breath holding in expiration is too difficult for the patient, then the patient is asked to hold their breath in a relaxed inspiration instead (Figure 1.2).

Several studies have been performed to explore the clinical significance of the different MRI parameters derived from cine imaging. In a recent study, RV mass was used as a study endpoint in the comparison of the effects of sildenafil and bosentan [22]. The results of this study showed that sildenafil reduced RV mass more than bosentan. However, the interpretation of these study findings is difficult, since a change in RV mass may reflect a change in PA pressure, or may be a sign of a normal adaptation to the disease [23]. Indeed,
a recent study investigating the prognostic value of different MR parameters at baseline and their change during therapy in 64 idiopathic PAH patients showed that the prognostic value of RV mass is limited in comparison to RV end-diastolic volume and stroke value [24]. A decrease in right ventricle end-diastolic volume and an increase in stroke volume during therapy reflected an excellent long-term prognosis in this study. The finding that RV end-diastolic volume is an important parameter to look for during therapy is in agreement with an earlier echocardiographic study [20]. The curvature of the IVS can also be calculated from these short-axis cines and this was shown to have a close relationship with the PA pressure [25]. To derive indices of RV diastolic function, additional long-axis cine images are required with sufficient temporal resolution (of the order of 15 ms) to visualise the pulmonary and tricuspid valves in cine mode. Although the investigation of the diastolic function of the RV has until now been limited, one study indicates that RV diastolic dysfunction is a measure of disease severity in PAH, and can be improved by medication [26] (Figure 1.3).

**PULMONARY ARTERY FLOW AND DISTENSIBILITY**

In order to obtain the flow characteristics of the PA, phase-contrast flow quantification in the main PA, in an image plane perpendicular to the main PA, is required (Figure 1.4).

The flow pattern in the PA contains significant information on the characteristics of the pulmonary vascular bed [27], although this has been poorly studied by MRI. In addition,
stroke volume can be calculated from the integrated area under the flow curve. Two MRI-based studies using stroke volume measurements derived from the pulmonary flow curve showed that stroke volume can be used to monitor therapy and contains important prognostic information [24, 28].

Another characteristic of the pulmonary vascular bed is the distensibility of the large pulmonary vessels. A recent study showed that increased stiffness of these vessels assessed by MRI is associated with a poor outcome in PAH [29] (Figure 1.5).

**MR PULMONARY ANGIOGRAPHY AND PERFUSION MEASUREMENTS**

Although digital subtraction angiography of the PA is still regarded as the reference technique for the diagnosis of chronic thromboembolic PH, recent studies showed that MR angiography is a sensitive non-invasive alternative for the depiction of central thromboembolic material [30]. Typically, one static 3D image acquisition is performed, tailored for spatial resolution and signal-to-noise during a breath hold of about 15 seconds. The advantage of MRI is not only that it provides high quality 3D images of the pulmonary vasculature, but also that these measurements can be combined with the assessment of RV function and
perfusion measurements [31]. MRI-based dynamic pulmonary perfusion imaging is a technique visualizing the passage of a contrast bolus of MRI contrast agent through the lungs in a 3-dimensional way, enabling the visualisation of subsegmental perfusion defects in chronic thromboembolic PAH [32]. In addition, post-processing of the perfusion images make it possible to quantify regional pulmonary blood flow, blood volume and mean transit time [33] (Figure 1.6).

**NEW DEVELOPMENTS**

The MRI protocol can be extended with more advanced techniques that have recently been used for the study of the RV in PAH. Examples are delayed contrast enhancement imaging and myocardial tagging. Delayed contrast enhancement imaging is performed about 10 minutes after injection of MRI contrast agent. In healthy myocardium, the contrast agent has washed out, but in non-viable myocardium the contrast agent is still present in the damaged and fibrotic tissue. Thus, ‘bright is dead’ with this technique. In a study in PAH, delayed contrast enhancement was observed at the insertion regions of the RV to the septum and LV wall [34]. Presumably, this delayed enhancement is a manifestation of regional myocardial injury.

Myocardial tagging is a MRI method to label the myocardial tissue with parallel lines or a grid (typical distance 7 mm) of magnetic presaturation at the beginning of the cardiac cycle. These lines remain visible as ‘dark’ lines in MRI cine images and thereby display the myocardial strain over the cardiac cycle by changes in the line- or grid-pattern. In PAH, the

![Figure 1.5](image-url)
RV myocardial wall is thick enough to explore with this tagging technique. In a study in PAH patients, it was shown that there is a left to right asynchrony in the peak of circumferential shortening, which is caused by RV overload and plays a role in the leftward septal bowing and impaired LV filling [35].

**COMPUTED TOMOGRAPHY (CT)**

CT scanning is a rapidly evolving technique in cardiovascular imaging. Recent technical advances such as the development of multislice CT (MSCT) and multidetector-row CT make it possible to measure RV volumes and function in an acceptable period of time [36, 37]. Although the main role of CT in phenotyping PH is well established, the role of CT in the longitudinal assessment of PAH is largely unexplored. However, it is reasonable to expect a similar imaging quality of the right ventricle with the now widespread availability of 64-slice scanners, permitting ECG-gated cardiac imaging and cardiac function in comparison to MRI. An advantage of multidose CT over MRI is that imaging of the right ventricle, pulmonary vessels and perfusion can be combined with high resolution imaging of the lung parenchyma in an acceptable timescale. A disadvantage of this technique is the high radiation doses required. At this point in time, the application of MSCT in the study of the right ventricle and PH remains limited.
REFERENCES