# Cardio-pulmonary MRI for Diagnosis and Monitoring of Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

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## Introduction

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a disease causing shortness of breath that could ultimately be life threatening but is potentially curable [1, 2]. Mean survival is less than 2 years in untreated CTEPH patients who have mean pulmonary artery pressure (mPAP) higher than 30 mmHg at diagnosis [3].

Currently there is a diagnostic algorithm for CTEPH diagnosis according to the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension [4]. The diagnosis of pulmonary hypertension (PH) requires a clinical suspicion based on symptoms, physical examination and review of a comprehensive set of investigations to confirm that hemodynamic criteria are met and to describe the etiology, the functional and hemodynamic severity of the condition. The interpretation of these investigations requires, at the very least, expertise in cardiology, imaging and respiratory medicine and may best be discussed at a multidisciplinary team meeting [4]. Echocardiography is initially used to confirm a general diagnosis of PH. Then ventilation/perfusion scanning (V/Q- SPECT) is the recommended clinical standard to confirm or rule out CTEPH diagnosis. This should be followed by right heart catheterization (RHC) which is the gold standard for PH diagnosis. RHC is ideally coupled with conventional pulmonary angiography, the technique for confirming the location and extent of disease that is mandatory for treatment planning [4]. Further workup of CTEPH patients may include pulmonary angiography computed tomography or cardio-pulmonary MRI.

Within the last decade cardio-pulmonary MRI has been introduced into the clinic and its acceptance as a tool to diagnose CTEPH and monitor treatment of patients with CTEPH is rapidly increasing [5, 6]. As a non-invasive imaging technique that does not involve ionizing radiation, it is the standard of reference for biventricular functional evaluation that can provide comprehensive functional-, perfusion- and hemodynamic-evaluation of the cardio-pulmonary unit in the setting of CTEPH.

## MRI-derived cardiac function and volumetry in CTEPH

Cine cardiac MR acquisitions have been established as the non-invasive gold standard for assessment of biventricular structure and function due to their inherent spatial resolution and freedom from acoustic window compared to echocardiography [7]. In CTEPH patients cardio-pulmonary MRI should include stacks of cine short axis and long axis images of both ventricles. These acquisitions allow reproducible and accurate biventricular size, function, volume and mass quantification. This is of particular importance in patients with pulmonary artery hypertension where right ventricular (RV) function is related to patient survival [8].

Typical signs for PH-related right heart strain are right RV dilatation, hypertrophy, right atrial dilatation and septal bowing [9]. RV hypertrophy is a remodeling mechanism in response to increased pulmonary pressure, which becomes insufficient to compensate increased afterload in the long term. It has been shown that in PH RV mass, wall thickness, and the ventricular mass index (VMI = ratio of RV mass to left ventricular (LV) mass) measured

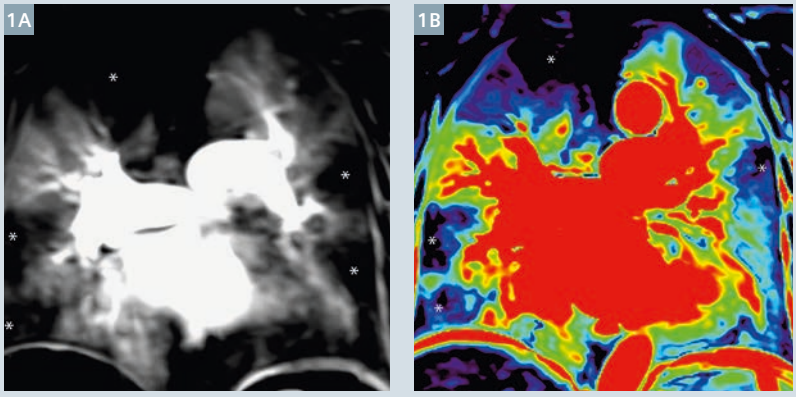
## Key Points

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a disease causing shortness of breath that could ultimately be life threatening. Within the last decade cardio-pulmonary MRI has been introduced into the clinic and its acceptance as a non-invasive, radiation-free tool to diagnose and monitor treatment of patients with CTEPH is rapidly increasing. It is the standard of reference for biventricular functional evaluation that can provide a comprehensive assessment of the cardio-pulmonary unit. In this article, we provide an overview of diagnosis and management of CTEPH patients by MRI-derived assessment of the cardiopulmonary unit.

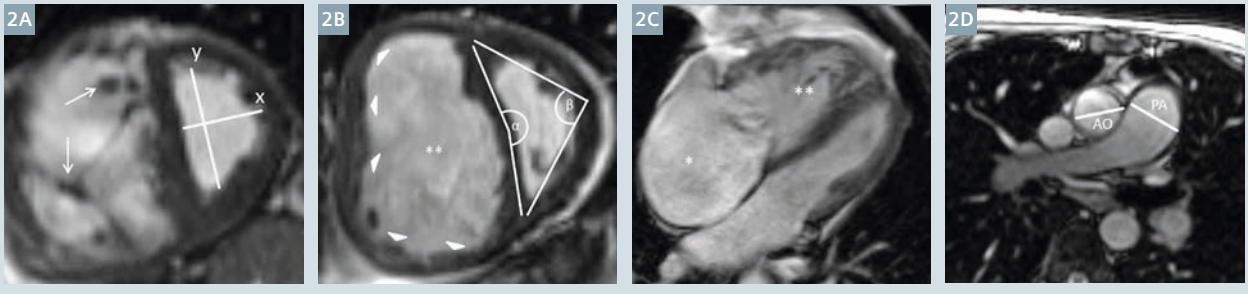
by cardio-pulmonary MRI are increased and correlate to increased afterload [10]. In addition, VMI has a high diagnostic accuracy for the detection of PH demonstrated by Swift et al. in the ASPIRE study [11]. Impaired RV diastolic function results in increased diastolic RV pressures and tricuspid regurgitation, inducing elevated right atrial pressures and dilatation Increased right atrial pressure is related to PH patient outcome [8]. The interventricular septum forms a functional unit between both ventricles. Under normal circumstances the septum has a rightward convexity that maintains during the cardiac cycle. In PH patients increased RV pressure shifts the septum toward the left, affecting LV filling that is generally reflected by low LV end-diastolic volumes in PH patients [12]. Eccentricity index and interventricular septal angle are parameters to quantify septal deformation [13, 14]. This septal bowing demonstrates strong correlation with the degree of pulmonary hypertension and is associated with worse prognosis in PH patients [15, 16].

## Pulmonary vessels and perfusion

Two different approaches are available for MR angiography (MRA) acquisition: A high spatial resolution contrast enhanced GRE MRA (CMRA) acquiring a single 3D data set, or a time resolved 3D MRA (DCE-MRI) using e.g. TWIST sequences [17]. Using CMRA, a classic pattern of peripheral vascular pruning with central pulmonary artery dilatation is observed in PH patients. This central pulmonary artery dilatation can be used as an imaging marker for PH detection [18]. Additionally, in CTEPH patients, typical findings observed on CMRA are: intraluminal webs and bands, vessel cut-offs and organized pulmonary artery wall-adherent thrombus that can be assessed up to the segmental vessels. In the setting of acute pulmonary embolism, CMRA demonstrated only a sensitivity of 79% (50 of 63) for detecting pulmonary embolism in a main or lobar pulmonary artery, shown in the PIOPED III study [19]. In the setting of chronic thromboembolism DCE-MRA allows identification and localization of regional hypoperfused lung parenchyma and thus differentiation between CTEPH and other forms of PH [20, 21]. It is usually performed after contrast bolus injection with use of parallel imaging techniques that allows a temporal resolution of 1 second covering the whole lung. Using this method Rajaram et al. showed in a single center registry study with 132 patients with a clinical suspicion for CTEPH from July 2013 that DCE-MRI has at least a similar sensitivity (97%), specificity (92%)




**1** Corresponding lung maps of a patient with chronic thromboembolic pulmonary hypertension (CTEPH) by 4D dynamic contrast enhanced (DCE) MRI at phase of maximum pulmonary parenchymal contrast **(1A)** and quantified by model independent deconvolution (pulmonary parenchymal blood flow (PBF)) **(1B)**. CTEPH characteristic wedge shaped areas of hypoperfusion (*) can be seen bipulmonal both in the DCE- and the PBF-maps.

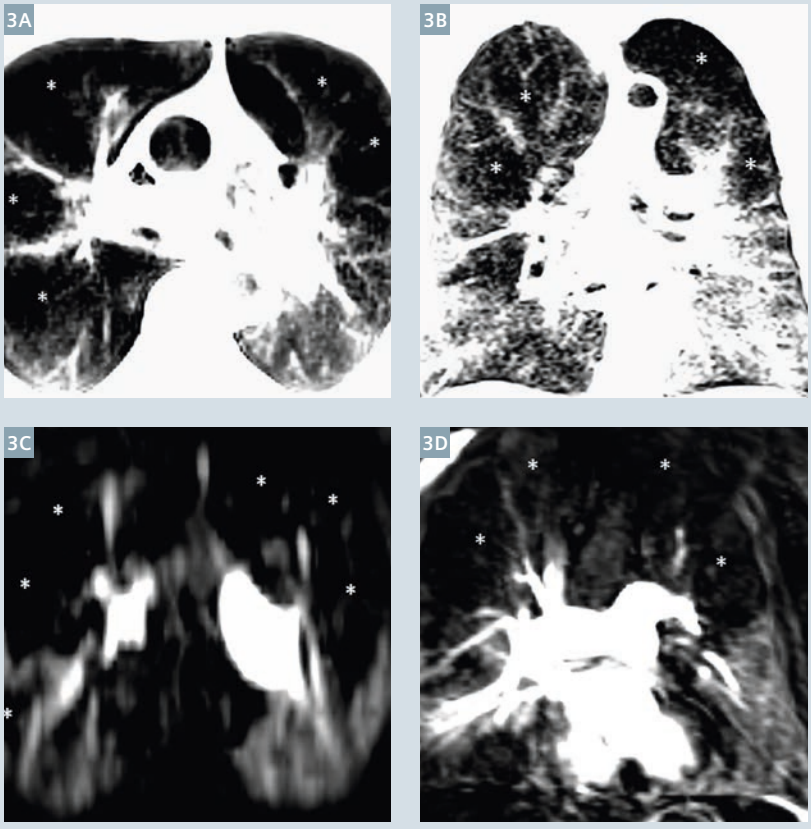



**2** Cine true fast imaging with steady state precession (TrueFISP) sequences in short axis view **(2A, B)** and four-chamber-view **(2C)** as well as TrueFISP sequence of ascending aorta (AO) and main pulmonary artery (PA) of a patient with chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary hypertension (PH) causes right heart strain and dilatation of pulmonary vessels **(2D)**. MRI signs for PH are hypertrabeculation (arrows), right ventricular hypertrophy (arrowheads), dilated right ventricle (**) and dilated right atrium (*). Septal defomation due to elevated right sided volume and pressure can be quantified by the eccentricity index (y/x>1.5 = pathological) or by interventricular septal angle measurements (2B).

and accuracy (94%) compared to scintigraphy (96% / 90% / 94%) to diagnose CTEPH with conventional angiography as the reference standard [20]. An in-place diagnostic multicenter study to proof the equality of cardio-pulmonary MRI to diagnose CTEPH compared to VQ-SPECT is currently on its way (www.change-mri.de).

In addition, DCE-MRI is capable of absolute quantification of regional parenchymal blood flow. Using pixel-by-pixel deconvolution analysis of the first pass bolus Pulmonary parenchymal Blood Flow (PBF)-, Pulmonary Blood Volume-, and Mean Transit Time (MTT)-maps can be calculated from the dynamic MRI data [22]. Pulmonary PBF correlates with mPAP and pulmonary vascular resistance as well as MTT in patients with CTEPH and PH [23, 24]. Additionally, DCE-MRI can assess the gravity dependent distribution, usually seen in healthy persons [25], which is reduced in CTEPH patients and normalizes after PEA as a result of improved hemodynamics [23].

One challenge in the evaluation of CTEPH is the differentiation between lung parenchymal changes and CTEPH related hypoperfusion. Multiple etiologies, such as atelectasis or emphysema, are able to potentially mimic CTEPH like hypoperfusion [26]. However, there are clinically established sequences for evaluation of parenchymal and thoracic changes like T2 half Fourier acquisition single shot turbo spin echo (HASTE) and true fast imaging with steady state precession (TrueFISP) sequences, which may increase specificity when evaluated together with the DCE-MRI for CTEPH diagnosis [17, 20]. Recently, 3-dimensional ultrashort echo-time (UTE) sequences with high spatial resolution have been established, which improve lung tissue evaluation with close to lung CT quality [27].

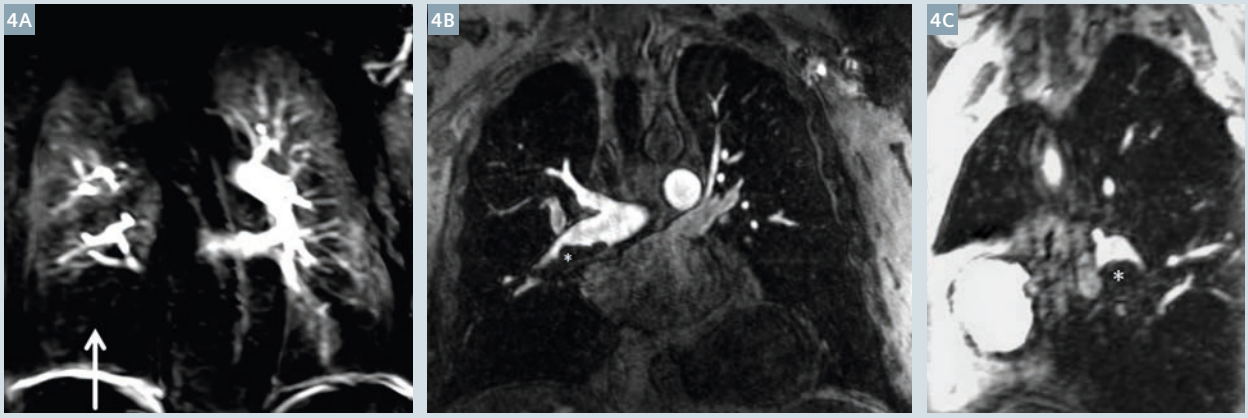



3 Anatomical images **(3A, B)** and dynamic contrast enhanced perfusion images **(3C, D)** in axial (3A, C) and coronal plane (3B, D) of a patient with chronic obstructive pulmonary disease negative for chronic thromboembolic pulmonary hypertension (CTEPH). Anatomical images (3A, B: T2 half Fourier acquisition single shot turbo spin echo) support discrimination between etiologies of hypoperfusion. In this patient areas of hypoperfusion (* in 3C, D) match with areas of emphysema (* in 3A, B) and in addition are not wedge shaped.

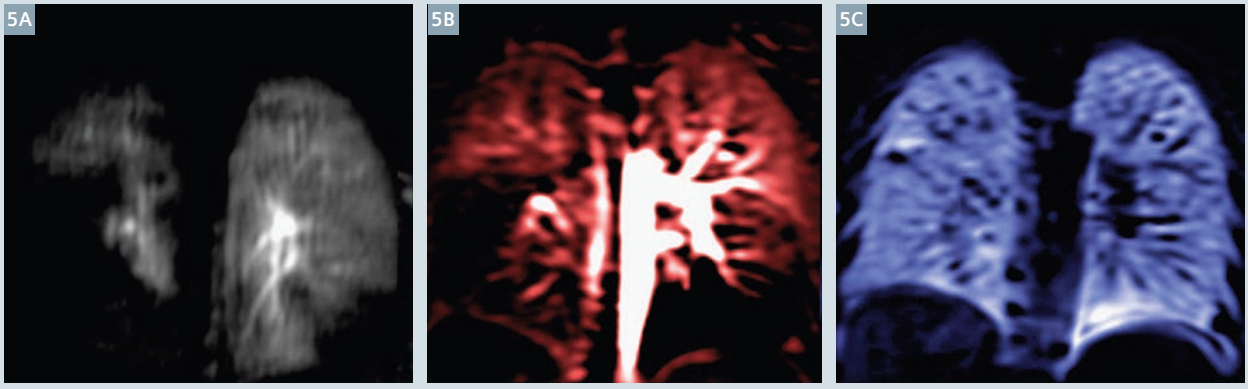
## Encouraging expectations

One very promising development in MR evaluation of the lung is non-contrast-enhanced, proton-based lung ventilation and perfusion MRI. This approach, known as Fourier decomposition (FD) MRI, utilizes routine TrueFISP or fast low-angle shot gradient-echo (FLASH) sequences for acquisition of lung images with subsequent compensation for respiratory motion by using non rigid image registration. Spectral analysis of the dynamic image series allows identification of peaks at the respiratory and cardiac frequencies. The amplitude of these peaks is related to regional proton density changes caused by deformation of lung parenchyma and pulmonary blood flow. Further image post-processing produces ventilation- and perfusion-weighted maps for regional assessment of lung ventilation and perfusion from a single acquisition series [28].

FD-MRI derived lung perfusion and ventilation correlated well to V/Q-SPECT findings in a porcine model [29]. Furthermore FD-MRI showed promising results in humans to detect the presence or absence of chronic pulmonary embolism on a per patient basis [21]. Thus the FD-MRI-method could be a possible future alternative to V/Q-SPECT for CTEPH diagnosis in free-breathing without exposure to ionizing radiation.




4 Time-resolved 3D MRA (DCE-MRI) **(4A)** and high spatial resolution contrast enhanced GRE MRA (CMRA) **(4B)**. CMRA provides detection of intraluminal webs and bands, vessel cut-offs and organized central thrombus (*) causing hypoperfusion of associated pulmonary parenchyma (arrow).




5 Corresponding Time-resolved 3D MRA (DCE-MRI) **(5A)**, perfusion-weighted (pw) Fourier Decomposition (FD) map **(5B)** and ventilation-weighted (vw) Fourier Decomposition (FD) map **(5C)** of a patient with chronic thromboembolic pulmonary hypertension (CTEPH). Hypoperfusion is proven in both lower lobes on the DCE-MRI and in the pw-FD-map. Ventilation/perfusion mismatch predominantly in the lower lobes is typical for CTEPH patients.

## Conclusion

A comprehensive one-stop-shop cardio-pulmonary MRI exam has a promising future for detection and monitoring of CTEPH patients. Ventilation and perfusion weighted FD imaging of the lung is an especially promising technique of an MRI V/Q scan without contrast agent or radiation.

[1] WIP, the product is currently under development and is not for sale in the US and in other countries. Its future availability cannot be ensured.

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