Validation of Automated Perfusion-Weighted Phase-Resolved Functional Lung (PREFUL)-MRI in Patients With Pulmonary Diseases

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Background: Perfusion-weighted (Qw) noncontrast-enhanced proton lung MRI is a promising technique for assessment of pulmonary perfusion, but still requires validation.

Purpose: To improve perfusion-weighted phase-resolved functional lung (PREFUL)-MRI, to validate PREFUL with perfusion single photon emission computed tomography (SPECT) as a gold standard, and to compare PREFUL with dynamic contrast-enhanced (DCE)-MRI as a reference.

Study Type: Retrospective.

Population: Twenty patients with chronic obstructive pulmonary disease (COPD), 14 patients with cystic fibrosis (CF), and 21 patients with chronic thromboembolic pulmonary hypertension (CTEPH) were included.

Field Strength/Sequence: For PREFUL-MRI, a spoiled gradient echo sequence and for DCE-MRI a 3D time-resolved angiography with stochastic trajectories sequence were used at 1.5T.

Assessment: PREFUL-MRI coronal slices were acquired in free-breathing. DCE-MRI was performed in breath-hold with injection of 0.03 mmol/kg bodyweight of gadoteric acid at a rate of 4 cc/s. Perfusion SPECT images were obtained for six CTEPH patients. Images were coregistered. An algorithm to define the appropriate PREFUL perfusion phase was developed using perfusion SPECT data. Perfusion defect percentages (QDP) and Qw-values were calculated for all methods. For PREFUL quantitative perfusion values (PREFULQ) and for DCE pulmonary blood flow (PBF) was calculated.

Statistical Tests: Obtained parameters were assessed using Pearson correlation and Bland–Altman analysis.

Results: Qw-SPECT correlated with Qw-DCE (r = 0.50, P < 0.01) and Qw-PREFUL (r = 0.47, P < 0.01). Spatial overlap of QDP maps showed an agreement ≥67.7% comparing SPECT and DCE, ≥64.1% for SPECT and PREFUL, and ≥60.2% comparing DCE and PREFUL. Significant correlations of Qw-PREFUL and Qw-DCE were found (COPD: r = 0.79, P < 0.01; CF: r = 0.77, P < 0.01; CTEPH: r = 0.73, P < 0.01). PREFULQ/PBF correlations were similar/lower (CF, CTEPH: P > 0.12; COPD: P < 0.01) compared to Qw-PREFUL/DCE correlations. PREFULQ-values were higher/similar compared to PBF-values (COPD, CF: P < 0.01; CTEPH: P = 0.026).

Data Conclusion: The automated PREFUL algorithm may allow for noncontrast-enhanced pulmonary perfusion assessment in COPD, CF, and CTEPH patients comparable to DCE-MRI.

Level of Evidence: 3
Technical Efficacy: Stage 2

View this article online at wileyonlinelibrary.com. DOI: 10.1002/jmri.27027
Received Sep 12, 2019, Accepted for publication Dec 2, 2019.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), cystic fibrosis (CF), and chronic thromboembolic pulmonary hypertension (CTEPH) are life-shortening diseases causing impairment of pulmonary ventilation and perfusion. To improve patient outcome, development of methods to detect and monitor the above-mentioned diseases is the goal of current research. In this regard, imaging methods such as computed tomography (CT), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) play a clinical role in visualization of pulmonary structure and function.

For diagnosis of CTEPH, planar scintigraphy or SPECT ventilation/perfusion (V/Q) scans are recommended. However, SPECT requires the injection of a radiopharmaceutical, resulting in exposure to gamma radiation.

MRI is an ionizing radiation-free imaging modality and recent studies have found comparable diagnostic accuracy of dynamic contrast-enhanced (DCE)-MRI against planar scintigraphy and SPECT V/Q scans in CTEPH. DCE-MRI is an established technique for assessment of lung perfusion, but still requires the administration of gadolinium-based intravenous contrast agents. These are reported to cause side effects like nephrogenic systemic sclerosis in patients with renal failure and gadolinium deposition in different parts of the body. Furthermore, a breath-hold is required for DCE data acquisition. Therefore, validation of free-breathing non-contrast 1H MRI postprocessing techniques like Fourier decomposition (FD) and phase resolved functional lung (PREFUL)-MRI is desirable.

The principle of FD is the registration of dynamic images to facilitate analysis on a voxel level, followed by Fourier transformation of the signal time series for distinct analysis of the respiratory and cardiac frequency component. Thus, simultaneous assessment of lung ventilation and perfusion is possible.

PREFUL-MRI is a further development of the FD post-processing technique, which includes the reconstruction of a full respiratory and cardiac cycle. Dynamic information about ventilation and perfusion is derived, which may be sensitive for detection of early disease. However, further validation of PREFUL-MRI is needed.

Thus, the purpose of this study was to test the following hypotheses:

1. A specific phase of the reconstructed cardiac cycle of PREFUL-MRI can be identified, which reflects pulmonary perfusion, as validated by perfusion SPECT. Further, this PREFUL phase correlates with a phase of DCE-MRI.
2. PREFUL-MRI and DCE-MRI provide comparable information in COPD, CF, and CTEPH patients.

Materials and Methods

Patient Characteristics and Methods

This study was approved by the local Ethics Committee and written informed consent was obtained from all patients.

Twenty patients with COPD (age range 46–76 years, three females), 14 patients with CF (age range 5–22 years, 11 females), and 21 patients with CTEPH (age range 43–82 years, nine females), were included in this retrospective study (Fig. 1). For the COPD group, inclusion criteria were ≥40 years with clinical diagnosis of COPD and hyperinflation (residual volume >135% predicted). Included COPD patients are a subgroup of a previous study. For the CF group, patients with a confirmed diagnosis of CF in a clinically stable condition and a forced expiratory volume in 1 second (FEV₁) ≥40% predicted for age and gender were included. Part of the CF patients are a subgroup of a previously described study. For the CTEPH group, patients with diagnosed CTEPH were included. All patients were diagnosed by the local Department of Respiratory Medicine. Exclusion criteria were an incomplete MRI protocol and contraindications to MRI and MRI contrast agents.

All patients underwent DCE-MRI and PREFUL-MRI in the same imaging session with a 1.5T scanner (Avanto or Aera, Siemens Healthcare, Erlangen, Germany).

In addition, six of the CTEPH patients underwent perfusion SPECT imaging less than 4 months prior to the MRI scan. These six CTEPH patients will be referred to as the method development group. Using this group, algorithms to select a PREFUL and DCE phase were developed and applied to test the first hypothesis. The agreement of these selected phases of PREFUL and DCE was tested in all COPD, CF, and CTEPH patients (including the six CTEPH patients from the method development group), who will be referred to as the clinical application group.

Image Acquisition

SPECT. SPECT imaging was performed on a Siemens NM Symbia T₂ system. After injection of about 150 MBq of ⁹⁹mTc-HSA, imaging was performed with the patient in the supine position. In SPECT mode, 64 projections (energy window of 140.5 keV ±10%, matrix: 128 × 128) were acquired in one bed position. The acquisition time per projection was 10 seconds. CT for attenuation correction was acquired using a low-dose protocol under free breathing. Reconstruction was performed using an iterative ordered-subsets expectation maximization algorithm (OSEM).

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**Included patients (n = 55)**

| Diagnosis of COPD (n = 20) | Diagnosis of CF (n = 14) | Diagnosis of CTEPH (n = 21) |
|----------------------------|--------------------------|-----------------------------|
| MRI protocol complete (n = 20) | MRI protocol complete (n = 14) | MRI protocol complete (n = 21) |
| additional SPECT (n = 6) |                          |                             |

FIGURE 1: Patient cohort.
**PREFUL-MRI.** For PREFUL-MRI three coronal slices, with the midslice centered on the tracheal bifurcation, were acquired using a spoiled gradient echo sequence with the following settings: field of view (FoV) 340 × 340 mm² to 500 × 500 mm², matrix size 128 × 96 to 128 × 128 (all interpolated to 256 × 256), slice thickness 15 mm, 15–36 mm gap between slice positions, echo time (TE) 0.67–0.91 msec, repetition time (TR) 3 msec, flip angle 5–8°/C14, bandwidth 1085–1502 Hz/px, temporal resolution 192–289 msec. For each patient, 200 or 250 images per slice were obtained.

**DCE-MRI.** DCE-MRI was acquired in a single breath-hold at end inspiration using a 3D time-resolved angiography with a stochastic trajectories (TWIST) sequence with the following settings: FoV 276 × 340 mm² to 421 × 500 mm², matrix size 192 × 113 to 256 × 146, slice thickness 3–6 mm, TE 0.7–0.89 msec, TR 2.13–2.74 msec, flip angle 10–30°/C14, bandwidth 570–744 Hz/px, temporal resolution 0.8–1.1 sec. A bolus of 0.03 mmol/kg bodyweight of gadoteric acid was injected at a rate of 4 cc/s.

**Postprocessing**

**PREFUL-MRI.** All images were registered towards one fixed image in intermediate lung position using the group-oriented registration approach²⁰ and the freely available Advanced Normalization Toolkit (ANTs²¹). Modifications were made to the previously described postprocessing¹⁵ steps for calculating lung perfusion: Using the registered images, with assistance of a semantic convolutional neural network,²² a semiautomatic segmentation of the lung boundaries was performed. To obtain a signal time series for phase sorting, spatial averaging over a region of interest (ROI) consisting of blood voxels (eg, pulmonary vessels, the aorta, or the heart) has to be performed. Instead of using a manual segmented ROI inside the aorta, the following automated algorithm searched for an optimized ROI (R_sort) located inside a central pulmonary artery, the aorta, or inside the heart (Fig. 2):

1. The left and right lung and the mediastinum were included in a search ROI (Aₚ).
2. A high-pass filter at 0.75 Hz was applied to all registered images and for all voxels within Aₚ, the standard deviation of all images was computed to get a simplified perfusion weighted map (M_std).
3. Since high-intensity values are expected in perfused vessels, a temporal maximum intensity projection map (M_MIP) for all voxels inside Aₚ was calculated.
4. All voxels above the 98th percentile of M_std and above the 98th percentile of M_MIP were chosen for R_sort.
5. As a result, R_sort consisted of several voxel clusters.

To avoid different cardiac phases in the voxel clusters and to improve the sine fit, R_sort was iteratively adjusted by comparing the goodness of fit parameter R² of the sine fit before and after removing a cluster. If the sine fit improves, the cluster will be removed from R_sort. As a lower limit, at least one cluster had to remain in R_sort.

Finally, images were sorted according to their perfusion phase and interpolated to 15 phases at an equidistant time grid covering one cardiac cycle. R² values of the sine fit were calculated for further analysis.

**SLICE AND VOXEL ALIGNMENT OF DCE, SPECT, AND PREFUL.** A coronal slice of the SPECT image corresponding to the morphological PREFUL image was selected visually. Due to thinner slice thickness of DCE-MRI in comparison with PREFUL-MRI, a compound coronal DCE slice corresponding...
to the PREFUL image was calculated as follows: First, DCE slices were multiplied by a normalized slice-overlap weighting factor. Then the compound slice was obtained by summation over the weighted DCE slices.

Using rigid transformations, DCE and PREFUL images were registered onto the corresponding SPECT image. For comparison between PREFUL- and DCE-MRI, PREFUL images were also registered to DCE images using a combination of rigid and nonrigid transformation.

**LUNG SEGMENTATION OF DCE, SPECT, AND PREFUL.** Excluding large vessels, both lungs were segmented manually for further postprocessing. The registration enabled using the same segmentation masks for further PREFUL, DCE, and SPECT perfusion analysis.

**PHASE SELECTION OF DCE AND PREFUL.** For further analysis, a phase selection of the reconstructed cardiac cycle derived by PREFUL and of the contrast agent pass of the DCE dataset was performed. The phase selection was either extracted from the PREFUL and DCE data itself or guided by the SPECT image. The latter was performed similarly for PREFUL- and DCE-MRI. Within the segmented lung parenchyma ROI, all temporal phases were correlated voxel-by-voxel with the SPECT image using Pearson correlation. The phase with the highest correlation was used as the gold standard PREFUL (PREFUL-SPECT) or DCE (DCE-SPECT) phase.

In addition, for PREFUL-MRI the following stand-alone phase selection algorithm was applied: For every voxel inside the lung parenchyma ROI the phase with the maximal intensity was determined and the most frequent phase was used as the PREFUL phase (PREFULalg). For CTEPH patients, to avoid the selection of a phase showing delayed perfusion, PREFULalg was restricted to be within the first eight phases. A more detailed explanation about the restriction for the CTEPH patients is given in the Discussion.

For DCE-MRI, the following stand-alone phase selection algorithm was used: As illustrated by Supporting Fig. 1, for DCE phase selection, an averaged time series over an ROI inside the aortic arch on the tracheal slice was computed, showing the contrast agent intensity over time. All timepoints prior to the bolus arrival in the aorta were defined as baseline. To ensure that the contrast agent has arrived in the aorta and hence has passed through the lung parenchyma, the first timepoint after baseline was selected as DCE phase (DCEalg).

**Comparison of PREFUL and DCE with SPECT**
For each slice, QDP maps were calculated for DCE and PREFUL phases as well as for the SPECT image using an individual threshold: As described previously,24 for PREFUL- and DCE-MRI, the 75th percentile of voxel values above zero of the perfusion-weighted maps inside the lung parenchyma was calculated and multiplied by 0.6. Values below this threshold were identified as perfusion defect. For SPECT, the threshold was defined as 40% of the maximum on the SPECT image. The same approach was used by Derlin et al, who validated this threshold with right-sided heart catheterization.25 All voxels below this threshold were identified as perfusion defect.

**Comparison of PREFUL and DCE**
For each slice, perfusion-weighted values of the DCE and PREFUL phases were compared voxel-by-voxel and by the median over the same several ROIs: the total lung parenchyma, the left and right lung, and the segmented lung parenchyma divided into quadrants.

Further, for each slice QDP maps of DCEalg and PREFULalg were calculated for the method development group and for the clinical application group using the threshold described above. For the latter, QDP maps were also calculated for the whole lung. In addition, QDP maps of each slice derived by DCESPECT and PREFUL-SPECT were obtained for the method development group.

**Statistical Analysis**
Since the Kolmogorov–Smirnov test was negative for all functional MRI parameters, nonparametric tests were used (alpha level 0.05). Unless noted otherwise, data are presented as median with 25th and 75th percentile.

For the method development group, R² values of the sine fits obtained by the new PREFUL sorting algorithm and the one previously described15 were compared using a paired two-sided Wilcoxon test. Phase differences of corresponding PREFUL-SPECT and PREFULalg phases as well as DCE-SPECT and DCEalg phases were calculated for every patient. The agreement of selected PREFUL phases and of DCE phases was assessed by using a paired two-sided Wilcoxon test.

DCESPECT, DCEalg, PREFUL-SPECT, and PREFULalg were compared with SPECT by Pearson correlation on a voxel-by-voxel level (alpha level 0.05).

Comparing PREFUL and DCE, Pearson correlation coefficients were calculated for the perfusion-weighted values of the DCE-SPECT and PREFUL-SPECT phases as well as of the DCEalg and PREFULalg phases on a voxel-by-voxel level for all the different ROIs of the lung parenchyma defined above.

For each cohort in the clinical application group, Pearson correlation of median PREFULalg and DCEalg values was performed for the different ROIs.

To assess the agreement between QDP maps, the Dice coefficients of the defect and healthy regions were calculated on a voxel-by-voxel level. Furthermore, the spatial overlap (ie, percentage of voxels labeled as perfusion defect or healthy tissue with both methods) was computed and compared using a paired two-sided Wilcoxon test. The agreement of QDP was further assessed by Bland–Altman analysis.

**Comparison of Quantitative PREFUL-MRI With Quantitative DCE-MRI**
To assess the potential of quantitative perfusion PREFUL-MRI, using the clinical application group, the PREFULalg phase was quantified using the approach given by Kjørstad et al26:

\[
\text{PREFUL}_Q = \frac{S_V}{S_{FBV}} \times \frac{1}{2 \times t_{pref}}
\]

where \(S_V\) is the signal intensity of every voxel, \(S_{FBV}\) is the signal intensity of a fully blood-filled voxel (FBV) determined for the tracheal slice and applied to all three slices, and \(t_{pref}\) is the time between two heartbeats and compared to pulmonary blood flow (PBF).
derived by DCE-MRI. To determine the signal intensity of the FBV, an averaged signal time series over Rsort was computed and the phase corresponding to the maximal signal was selected. SFBV is defined as the maximal intensity inside Rsort at this phase.

For DCE-MRI, PBF was calculated using a deconvolution algorithm, with the Volterra formula as discretization method and singular value decomposition of the convolution matrix with subsequent truncation of the smallest singular values as regularization.27,28 In this study, singular values below 15% of the largest singular value were removed (on average 73% of the singular values were removed). This empirical threshold was tested and validated previously.22 Median PREFULQ and PBF values were computed for all lung parenchyma ROIs and compared using Pearson correlation. Correlation coefficients were compared to those obtained by PREFULalg and DCEalg using a paired two-sided Wilcoxon test. Further, median PREFULQ and PBF values for the whole lung were assessed by Bland-Altman analysis and a paired two-sided Wilcoxon test was performed.

Results

Method Development Group

PREFUL SORTING ANALYSIS ACCORDING TO CARDIAC CYCLE. The coefficient of determination of the sine fit applied to sort the data according to the cardiac cycle significantly increased from R² = 0.78 (0.70–0.86) using the mean signal of a manually selected ROI inside the aorta15 to 0.88 (0.84–0.91) using the new automated algorithm presented in this work (P < 0.01).

PHASE SELECTION OF PREFUL AND DCE. Comparing the DCEspect and DCEalg phases, no significant mean phase difference (0.3 phases, standard deviation [SD] 0.5 phases, P = 0.50) was found. Similarly, for PREFUL-MRI no significant mean phase differences (1.4 phases, SD 1.6 phases, P = 0.55) was obtained.

COMPARISON OF PREFUL AND DCE WITH SPECT. For an exemplary CTEPH patient, in Fig. 3 a good visual agreement between SPECT and the corresponding DCEspect and PREFULspect phases with the resulting QDP maps and a map illustrating the spatial overlap of the QDP maps is shown.

Significant correlations were found between SPECT and perfusion-weighted DCE values (DCEspect: r = 0.50 (0.47–0.68), P < 0.01; DCEalg: r = 0.50 (0.47–0.68), P < 0.01) or perfusion-weighted PREFUL values (PREFULspect: r = 0.47 (0.34–0.56), P < 0.01; PREFULalg: r = 0.45 (0.20–0.50), P < 0.01).

In Table 1 and Supporting Table 1, QDP derived by SPECT (QDPSpect) is compared with QDP derived by

![Figure 3: Representative coronal maps of a SPECT image. The DCEspect and PREFULspect phases, found by correlation with the SPECT image (first row), the corresponding perfusion defect maps (QDP maps, second row) and maps showing the spatial overlap of the QDP maps derived by SPECT and DCE as well as by SPECT and PREFUL (third row) in a 59-year-old man with CTEPH; QDPSpect 63.4%, QDPDCE 56.6%, QDPPREFUL 63.9%, 76.2% overlap for DCE with a Dice coefficient of 0.80 for Q defect label and 0.70 for the healthy label; 80.8% overlap for PREFUL with a Dice coefficient of 0.85 for the Q defect label and 0.73 for the healthy label). For DCEspect and PREFULspect maps, 100% is the 95th percentile of all values above zero and inside the segmented lung parenchyma. DCEspect/PREFULspect, DCE/PREFUL phase obtained by correlation with SPECT image.](image-url)
No significant difference was found between spatial overlap obtained for both DCE phase selection methods (P ≥ 0.5) and for both PREFUL phase selection methods (P ≥ 0.25). Comparing QDP_DCE and QDP_SPECT, a significant difference was obtained for the posterior slice for both DCE phase selection methods (Fig. 4 and Supporting Fig. 2).

COMPARISON OF PREFUL AND DCE. As illustrated by Table 2, significant correlations were found comparing DCESPECT and PREFULSPECT (anterior: r = 0.55, P < 0.01) as well as DCEalg and PREFULalg (tracheal: r = 0.45, P < 0.01) on a voxel-by-voxel level.

In Supporting Table 2 and Supporting Fig. 3, QDP derived by the DCE and PREFUL phases are compared. Spatial overlap was similar for both phase selection methods (posterior: P = 0.25, tracheal: P = 0.13, anterior: P = 0.81).

Clinical Application Group

Figure 5 shows representative PREFULalg and DCEalg maps of a COPD, CF, and CTEPH patient, the corresponding QDP maps and maps illustrating the spatial overlap of the QDP maps, with good visual agreement.

As illustrated by Table 3, strong correlations of PREFULalg and DCEalg (r_{alg}) could be found for the COPD patients (anterior right lung: r = 0.79, P < 0.01). Slightly lower correlations were obtained for the CF patients (posterior upper right lung: r = 0.77, P < 0.01). For the CTEPH patients, a wide range of correlations was found (r = 0.04, P = 0.86; r = 0.73, P < 0.01).

In Table 4 and Fig. 6, QDP derived by DCEalg and PREFULalg are compared for all patient cohorts: QDP_{PREFUL} and QDP_{DCE} showed a spatial overlap ≥60.2% and slightly increased values for QDP_{PREFUL} (COPD: P = 0.1, CF: P = 0.02, CTEPH: P = 0.03).

Correlation coefficients obtained for PREFUL_Q and PBF (r_{Q}) are listed in Supporting Table 3. Comparing r_{alg} and r_{Q}, similar values were found for the CF (P = 0.15) and for the CTEPH patients (P = 0.12). For the COPD patients r_{alg} values were higher compared to r_{Q} values (P < 0.01).

Bland–Altman analysis for PREFUL_{Q} and PBF values showed increased perfusion values obtained by PREFUL_{Q} compared to PBF for COPD and CF (P < 0.01, Supporting Fig. 4a,b). For CTEPH, a wide range of differences of the perfusion values was present (P = 0.26, Supporting Fig. 4c).

Discussion

In this study we present an automated PREFUL perfusion algorithm, which allows for robust and more accurate perfusion phase sorting, which is an important step towards clinical translation of this technology. Further, we showed that a specific phase of the reconstructed cardiac cycle of PREFUL-MRI reflects pulmonary perfusion, as validated by perfusion

| Table 1. Comparison of Perfusion Defect Maps (QDP) of SPECT and PREFUL |
|------------------|------------------|------------------|------------------|
| SPECT (Reference) | PREFUL_{PREFUL}  | DC (Defect)      | DC (Healthy)     |
| QDP (%)           | Overlap (%)      | DC (Defect)      | DC (Healthy)     |
| P                 | 64.5             | (59.4–69.0)      | 69.3             | (65.6–75.8)      |
| t                 | 62.5             | (60.4–68.4)      | 75.3             | (69.2–80.2)      |
| a                 | 62.7             | (58.8–65.9)      | 68.7             | (67.1–74.0)      |
| r                 | 62.7             | (58.5–81.1)      | 68.7             | (67.1–74.0)      |
| DC, Dice coefficient 
| PREFUL_{SPECT}  | PREFUL_{PREFUL}  | PREFUL_{PREFUL}  |
| QDP maps derived by SPECT and PREFUL were compared for the method development group (six CTEPH patients). Data provided as median with 25th and 75th percentiles in parentheses.
SPECT. In addition, PREFUL-MRI and DCE-MRI provide comparable information in COPD, CF, and CTEPH patients.

An important part of the presented PREFUL algorithm is the automated phase sorting algorithm, which entails the following advantages: Especially for slices without large vessels, manual segmentation can be difficult. Further, it is not evident which ROI generates the best signal for phase sorting. By using the algorithm, we overcome these problems, as segmentation is not limited to one ROI in large vessels. An ROI consisting of several voxel clusters is iteratively adjusted for optimal phase sorting using the coefficient of determination as an optimization parameter. Further, for implementation in clinical routine an automated algorithm is preferable, as manual segmentation is time-consuming and requires user interaction. However, since the algorithm was only applied to three slices, further validation is needed.

Using a group of six CTEPH patients, phase selection algorithms for DCE and PREFUL were developed. Additional care is required during PREFUL stand-alone phase selection in the CTEPH cohort: In this patient group thrombotic material in single pulmonary arteries causes delayed perfusion of the dependent lung parenchyma. In patients with high thrombotic burden, most of the voxels of the lung parenchyma will reach their maximum signal intensity at a later phase of the PREFUL heart cycle, likely due to a slower pulse wave velocity in obstructed pulmonary arterial segments. The perfusion signal of this late phase does not correspond to perfusion of the healthy lung parenchyma and can lead to false perfusion defect detection. It is therefore necessary to limit the PREFUL phase selection algorithm in CTEPH to the first half of the cardiac cycle. Since obstruction of pulmonary arteries due to thrombotic material does not usually occur in COPD and CF, no limitation of the PREFUL phase selection algorithm is needed for those patient groups. However, the described limitation should be considered whenever artery occlusion due to thrombotic material is present.

In addition, registration artifacts might be introduced during registration of DCE and PREFUL images to the SPECT image.

A semiquantitative approach for perfusion assessment is the generation of binary perfusion defect maps. In this study, QDP maps derived by DCE and PREFUL showed a good spatial agreement with QDP maps derived by SPECT. This is in accordance with previous results of Bauman et al, who showed that perfusion-weighted and ventilation-weighted FD images agreed with SPECT/CT using visual scores in a porcine lung model. Deviations from SPECT may be explained by the fact that SPECT is acquired using free-breathing over
TABLE 2. Correlation of DCE and PREFUL Phases

|                  | Posterior | Tracheal | Anterior |
|------------------|-----------|----------|----------|
|                  | PREFUL\_SPECT/DCE\_SPECT | PREFUL\_alg/DCE\_alg | PREFUL\_SPECT/DCE\_SPECT | PREFUL\_alg/DCE\_alg | PREFUL\_SPECT/DCE\_SPECT | PREFUL\_alg/DCE\_alg |
| Whole slice      | 0.42 (0.31–0.52) | 0.39 (0.20–0.52) | 0.48 (0.30–0.64) | 0.45 (0.23–0.58) | 0.55 (0.37–0.58) | 0.43 (0.22–0.58) |
| Right lung       | 0.37 (0.18–0.56) | 0.31 (0.01–0.56) | 0.44 (0.15–0.54) | 0.38 (0.09–0.53) | 0.52 (0.41–0.63) | 0.41 (0.17–0.52) |
| Left lung        | 0.35 (0.27–0.49) | 0.34 (0.24–0.42) | 0.56 (0.47–0.71) | 0.53 (0.40–0.65) | 0.47 (0.37–0.77) | 0.51 (–0.10–0.75) |
| Upper right lung | 0.25 (0.18–0.32) | 0.20 (0.11–0.32) | 0.37 (0.03–0.53) | 0.40 (0.13–0.47) | 0.31 (–0.07–0.76) | 0.24 (–0.11–0.58) |
| Lower right lung | 0.24 (0.11–0.53) | 0.24 (0.10–0.53) | 0.21 (0.15–0.41) | 0.14 (0.07–0.46) | 0.41 (0.32–0.66) | 0.41 (–0.06–0.55) |
| Upper left lung  | 0.37 (0.19–0.46) | 0.26 (0.14–0.38) | 0.60 (0.28–0.63) | 0.48 (0.28–0.61) | 0.46 (0.36–0.71) | 0.42 (0.25–0.66) |
| Lower left lung  | 0.23 (0.13–0.33) | 0.30 (0.13–0.48) | 0.11 (0.02–0.17) | 0.06 (–0.02–0.15) | 0.23 (0.01–0.28) | –0.13 (–0.32–0.27) |

DCE and PREFUL phases of the method development group (six CTEPH patients) were compared using Pearson correlation on a voxel by level (P < 0.01 for most regions of interest). Data provide as median with 25th and 75th percentiles in parentheses. DCE\_SPECT/PREFUL\_SPECT, DCE/PREFUL phase obtained by correlation with SPECT image. DCE\_alg/PREFUL\_alg, DCE/PREFUL phase found by stand-alone phase selection algorithms.

FIGURE 5: Representative coronal maps of DCE\_alg and PREFUL\_alg phases, the corresponding perfusion defect maps (QDP maps), as well as comparison of match and mismatch of the QDP maps of both methods for first row: A 67-year-old man with COPD, QDP\_DCE 58.6%, QDP\_PREFUL 60.2%, 77.8% overlap with a Dice coefficient of 0.82 for Q defect label and 0.72 for the healthy label. Second row: A 17-year-old woman with CF, QDP\_DCE 32.5%, QDP\_PREFUL 47.9%, 66.6% overlap with a Dice coefficient of 0.59 for Q defect label and 0.72 for the healthy label. Third row: A 56-year-old man with CTEPH, QDP\_DCE 53.7%, QDP\_PREFUL 58.4%, 76.8% overlap with a Dice coefficient of 0.80 for Q defect label and 0.72 for the healthy label. For DCE\_alg and PREFUL\_alg maps, 100% is the 95th percentile of all values above zero and inside the segmented lung parenchyma. DCE\_alg/PREFUL\_alg, DCE/PREFUL phase found by stand-alone phase selection algorithms.
several minutes of acquisition time, causing motion blur and imprecise estimation of perfused volumes. In addition, limited spatial resolution of SPECT may also contribute to imprecise estimation of perfused volumes at SPECT due to partial volume effects.

A prerequisite to calculate QDP maps is the definition of the threshold to define healthy parenchyma: For DCE and PREFUL, the approach of Kaireit et al was used, who defined values below the 75th percentile multiplied by an empirical factor of 0.6 as perfusion defect. A similar approach was given by Bauman et al, who defined values below the median signal of the lung parenchyma multiplied by an empirical factor of 0.8 as perfusion defect. This modification was introduced to avoid underestimation of the perfusion defects, which is likely to occur in patients with severe perfusion impairment.

For SPECT, thresholds between 40% and 45% are widely accepted for nuclear medicine volumetry and used for

| TABLE 3. Correlation of DCE_{alg} and PREFUL_{alg} for COPD, CF, and CTEPH |
|-----------------|----------------|----------------|
|                 | COPD           | CF             | CTEPH          |
|                 | \( r \)        | \( P \)        | \( r \)        | \( P \)        | \( r \)        | \( P \)        |
| Whole lung      | 0.74           | <0.01          | 0.61           | **0.02**       | 0.31           | 0.18           |
| Posterior       |                |                |                |                |                |                |
| Right lung      | 0.55           | **0.01**       | 0.48           | 0.08           | 0.64           | <0.01          |
| Upper right lung| 0.66           | <0.01          | 0.77           | <0.01          | 0.28           | 0.22           |
| Lower right lung| 0.41           | 0.07           | 0.28           | 0.34           | 0.70           | <0.01          |
| Left lung       | 0.50           | **0.02**       | 0.53           | 0.05           | 0.05           | 0.84           |
| Upper left lung  | 0.68           | <0.01          | 0.68           | <0.01          | 0.51           | **0.02**       |
| Lower left lung  | 0.41           | 0.07           | 0.41           | 0.14           | 0.05           | 0.82           |
| Both lungs      | 0.55           | **0.01**       | 0.57           | **0.03**       | 0.04           | 0.86           |
| Tracheal        |                |                |                |                |                |                |
| Right lung      | 0.74           | <0.01          | 0.62           | **0.02**       | 0.73           | <0.01          |
| Upper right lung| 0.72           | <0.01          | 0.65           | **0.01**       | 0.67           | <0.01          |
| Lower right lung| 0.74           | <0.01          | 0.56           | **0.04**       | 0.71           | <0.01          |
| Left lung       | 0.71           | <0.01          | 0.50           | 0.07           | 0.29           | 0.21           |
| Upper left lung  | 0.74           | <0.01          | 0.37           | 0.19           | 0.23           | 0.33           |
| Lower left lung  | 0.46           | **0.04**       | 0.53           | 0.05           | 0.05           | 0.83           |
| Both lungs      | 0.75           | <0.01          | 0.59           | **0.03**       | 0.46           | **0.03**       |
| Anterior        |                |                |                |                |                |                |
| Right lung      | 0.79           | <0.01          | 0.61           | **0.02**       | 0.47           | 0.03           |
| Upper right lung| 0.74           | <0.01          | 0.38           | 0.18           | 0.39           | 0.08           |
| Lower right lung| 0.76           | <0.01          | 0.65           | **0.01**       | 0.47           | 0.03           |
| Left lung       | 0.64           | <0.01          | 0.36           | 0.20           | 0.49           | **0.02**       |
| Upper left lung  | 0.60           | <0.01          | 0.33           | 0.25           | 0.61           | <0.01          |
| Lower left lung  | 0.57           | <0.01          | 0.24           | 0.41           | 0.32           | 0.15           |
| Both lungs      | 0.77           | <0.01          | 0.55           | **0.04**       | 0.28           | 0.21           |

Using Pearson correlation, median perfusion values obtained by DCE_{alg} and PREFUL_{alg} were compared for the COPD, CF, and CTEPH patients. DCE_{alg}/PREFUL_{alg}, DCE/PREFUL phase found by stand-alone phase selection algorithms. Significant \( P \)-values printed in bold.
In this study, a threshold of 40% of the maximum on the SPECT image was used, as validated by Derlin et al.\textsuperscript{25} For the clinical application group as well as for the method development group, significant correlations between perfusion-weighted values of the PREFUL and DCE phases were found for most of the ROIs. This is in accordance with a recent study, which demonstrated a good agreement between FD and DCE-MRI in CF patients using visual and automated scoring of pulmonary perfusion.\textsuperscript{30}

No or low correlations, especially in the lower parts of the lung, might be explained by inaccurate registration, occurring mostly in the region around the diaphragm, which is predominantly affected by respiratory motion. Also, artifacts due to cardiac motion may have affected image quality. The lower correlations in the CTEPH patients might also be explained by more pronounced perfusion defects compared to COPD and CF caused by thrombotic material in single pulmonary arteries.

Comparing QDP maps derived by corresponding \textit{PREFUL\textsubscript{alg}} and \textit{DCE\textsubscript{alg}} phases a good spatial agreement was found for COPD, CF, and CTEPH patients. These results were in accordance with those reported in a recent study.\textsuperscript{24} Minor differences between QDP\textsubscript{DCE} and QDP\textsubscript{PREFUL} could be explained by the lower resolution of \textit{PREFUL} compared to DCE, causing widening and blurring of vessels, which may contribute to imprecise estimation of perfused areas.

| TABLE 4. Comparison of Perfusion Defect Maps (QDP) of \textit{DCE\textsubscript{alg}} and \textit{PREFUL\textsubscript{alg}} for COPD, CF and CTEPH |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | QDP DCE (%)     | QDP PREFUL (%)  | Overlap (%)     | DC (Defect)     | DC (Healthy)    |
| COPD            |                 |                 |                 |                 |                 |
| Whole lung      | 47.4 (40.8–55.3)| 47.8 (42.6–54.4)| 61.0 (59.8–63.3)| 0.57 (0.50–0.66)| 0.63 (0.59–0.69)|
| Posterior       | 43.7 (34.5–53.7)| 48.1 (41.6–56.4)| 64.1 (62.7–68.1)| 0.60 (0.52–0.69)| 0.66 (0.62–0.70)|
| Tracheal        | 47.0 (41.7–57.5)| 51.0 (45.8–56.5)| 60.7 (56.9–65.9)| 0.59 (0.53–0.67)| 0.61 (0.56–0.68)|
| Anterior        | 48.5 (43.7–58.2)| 44.2 (31.1–51.6)| 60.2 (55.1–65.2)| 0.55 (0.44–0.65)| 0.61 (0.56–0.69)|
| CF              |                 |                 |                 |                 |                 |
| Whole lung      | 36.9 (29.3–45.1)| 45.3 (40.7–47.7)| 63.8 (58.4–67.2)| 0.57 (0.41–0.60)| 0.67 (0.65–0.71)|
| Posterior       | 34.4 (28.1–45.7)| 40.6 (27.1–45.8)| 70.5 (66.8–77.5)| 0.60 (0.37–0.73)| 0.76 (0.73–0.8)|
| Tracheal        | 36.3 (27.4–41.2)| 44.3 (35.5–47.9)| 66.7 (63.1–70.0)| 0.60 (0.49–0.65)| 0.71 (0.69–0.76)|
| Anterior        | 34.5 (29.2–45.9)| 30.0 (20.1–37.3)| 60.9 (56.6–68.2)| 0.40 (0.32–0.46)| 0.71 (0.67–0.75)|
| CTEPH           |                 |                 |                 |                 |                 |
| Whole lung      | 55.6 (52.5–60.7)| 58.8 (56.2–62.0)| 69.5 (60.1–76.0)| 0.69 (0.65–0.78)| 0.61 (0.53–0.73)|
| Posterior       | 54.6 (52.5–59.8)| 57.7 (54.7–63.4)| 69.1 (60.0–73.2)| 0.71 (0.65–0.79)| 0.62 (0.52–0.68)|
| Tracheal        | 55.6 (51.8–59.8)| 57.1 (53.3–64.8)| 70.7 (60.3–75.9)| 0.74 (0.65–0.80)| 0.62 (0.51–0.72)|
| Anterior        | 54.6 (52.7–58.4)| 59.2 (54.0–65.1)| 67.1 (61.7–75.4)| 0.71 (0.67–0.79)| 0.61 (0.50–0.70)|

QDP-maps derived by \textit{DCE\textsubscript{alg}} and \textit{PREFUL\textsubscript{alg}} were compared for COPD, CF, and CTEPH patients. Data provided as median with 25\textsuperscript{th} and 75\textsuperscript{th} percentiles in parentheses. DC, Dice coefficient. \textit{DCE\textsubscript{alg}}/\textit{PREFUL\textsubscript{alg}}, \textit{DCE}/\textit{PREFUL} phase obtained by stand-alone phase selection algorithm.
Despite lower correlations between perfusion-weighted values of PREFUL and DCE in some ROIs, the good visual agreement between PREFULalg and DCEalg maps and the good agreement between PREFUL and DCE QPD maps for all patient cohorts make PREFUL-MRI a promising tool for assessment of COPD, CF, and CTEPH.

To assess the potential of quantitative PREFUL, PREFULQ values and PBF values derived by DCE were calculated. Comparing the correlation coefficients found between PREFULQ and PBF with those obtained by PREFULalg and DCEalg no significant difference was found for the CF and CTEPH patients. Further, PREFULQ values were significantly higher compared to PBF values for COPD and CF patients for the whole lung.

A series of reasons might lead to problems during PREFUL and FD quantification. Especially the correct estimation of SFBV for PREFUL quantification is difficult due to high signal variability inside Rsort. Further, signal strength can be influenced by $B_1$ field inhomogeneities, inaccuracies of the estimated receive coil sensitivities, and by the angle between the direction of the blood flow and the imaging plane. Moreover, the lower resolution of PREFUL causes widening and blurring of vessels in PREFULQ maps and therefore incorrect signal of lung parenchyma. Further, PBF values depend on the chosen quantification method and thus might contain errors.\(^\text{28,32}\) In addition, as shown by Fink et al.,\(^\text{33}\) the inspiratory level during breath-hold affects the computed PBF, with higher values at expiration. Since in this study, DCE datasets were acquired during a breath-hold in inspiration, computed PBF values might be underestimated.

**Limitations**

In this study, within PREFUL- and DCE-MRI, images were acquired with different spatial and temporal resolutions. For lower spatial resolution, partial volume effects are more pronounced, affecting the estimation of perfused areas for PREFUL and DCE. In addition, the interpolation process during PREFUL phase sorting depends on the temporal resolution. This might affect the consistency of the selected cardiac phase for perfusion analysis to a small degree. For DCE-MRI, higher temporal resolution leads to improved tracking of the contrast bolus pass through the lung parenchyma. As a result, determination of DCEalg can be more precise.

In addition, only three slices were examined using PREFUL-MRI, while DCE-MRI was a 3D sequence capable of imaging the whole lung. Further, only a small number of CF patients and patients receiving SPECT imaging were evaluated in this study.

For implementation of the presented PREFUL algorithm in routine clinical assessment of patients, it is important that the used registration and postprocessing approach is stable also for irregular breathing. This was shown previously.\(^\text{20}\) However, current challenges for clinical use of the PREFUL approach are automatization of postprocessing and a short evaluation time, as a complete and fast PREFUL analysis is desirable. In addition, implementation of PREFUL to higher fields might be of clinical interest. As recent studies showed, it is feasible to obtain FD-derived ventilation and perfusion-weighted information on 3T systems.\(^\text{20,34,35}\) [Correction added on January 7, 2020, after first online publication: Duplicate paragraphs regarding the limitations were deleted from the end of the Discussion and Limitations sections.]

**Conclusion**

The presented PREFUL perfusion algorithm may enable robust and automated regional pulmonary perfusion impairment measurement in COPD, CF, and CTEPH patients, which is a step towards clinical translation.

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