FULL PAPER

3D phase-resolved functional lung ventilation MR imaging in healthy volunteers and patients with chronic pulmonary disease

Filip Klimes\textsuperscript{1,2} | Andreas Voskrebenzev\textsuperscript{1,2} | Marcel Gutberlet\textsuperscript{1,2} | Agilo Luitger Kern\textsuperscript{1,2} | Lea Behrendt\textsuperscript{1,2} | Robert Grimm | Hendrik Suhling\textsuperscript{2,4} | Cristian Gonzales Crisosto\textsuperscript{1,2} | Till Frederick Kaireit\textsuperscript{1,2} | Gesa Helen Pöhler\textsuperscript{1,2} | Julian Glandorf\textsuperscript{1,2} | Frank Wacker\textsuperscript{1,2} | Jens Vogel-Claussen\textsuperscript{1,2}

\textsuperscript{1}Institute of Diagnostic and Interventional Radiology, Hannover Medical School, Hannover, Germany
\textsuperscript{2}Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Member of the German Centre for Lung Research (DZL), Hannover, Germany
\textsuperscript{3}Siemens Healthcare GmbH, Erlangen, Germany
\textsuperscript{4}Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany

Correspondence
Jens Vogel-Claussen, Institute of Diagnostic and Interventional Radiology, Hannover Medical School, OE 8220, Carl-Neuberg-Str. 1, 30625 Hannover, Germany. Email: vogel-claussen.jens@mh-hannover.de

Funding information
This work was funded by the German Center for Lung Research (DZL) and open access funding enabled and organized by Projekt DEAL.

Purpose: To test the feasibility of 3D phase-resolved functional lung (PREFUL) MRI in healthy volunteers and patients with chronic pulmonary disease, to compare 3D to 2D PREFUL, and to investigate the required temporal resolution to obtain stable 3D PREFUL measurement.

Methods: Sixteen participants underwent MRI using 2D and 3D PREFUL. Retrospectively, the spatial resolution of 3D PREFUL (4 × 4 × 4 mm\textsuperscript{3}) was decreased to match the spatial resolution of 2D PREFUL (4 × 4 × 15 mm\textsuperscript{3}), abbreviated as 3D\textsubscript{lowres}. In addition to regional ventilation (RVent), flow-volume loops were computed and rated by a cross-correlation (CC). Ventilation defect percentage (VDP) maps were obtained. RVent, CC, VDP\textsubscript{RVent}, and VDP\textsubscript{CC} were compared for systematic differences between 2D, 3D\textsubscript{lowres}, and 3D PREFUL. Dividing the 3D PREFUL data into 4- (≈ 20 phases), 8- (≈ 40 phases), and 12-min (≈ 60 phases) acquisition pieces, the ventilation parameter maps, including the heterogeneity of ventilation time to peak, were tested regarding the required temporal resolution.

Results: RVent, CC, VDP\textsubscript{RVent}, and VDP\textsubscript{CC} presented significant correlations between 2D and 3D PREFUL (\(r = 0.64-0.94\)). CC and VDP\textsubscript{CC} of 2D and 3D\textsubscript{lowres} PREFUL were significantly different (\(P < .0113\)). Comparing 3D\textsubscript{lowres} and 3D PREFUL, all parameters were found to be statistically different (\(P < .0045\)).

Conclusion: 3D PREFUL MRI depicts the whole lung volume and breathing cycle with superior image resolution and with likely more precision compared to 2D PREFUL. Furthermore, 3D PREFUL is more sensitive to detect regions of hypoventilation and ventilation heterogeneity compared to 3D\textsubscript{lowres} PREFUL, which is important for early detection and improved monitoring of patients with chronic lung disease.
1 INTRODUCTION

The measurement of regional pulmonary ventilation abnormalities is of great importance in patients with chronic lung diseases such as asthma, cystic fibrosis (CF), or chronic obstructive pulmonary disease (COPD). Despite the inherent limitations due to low proton density of the pulmonary parenchyma and susceptibility artifacts, proton MRI of the lung is gaining interest. Aside from its acquisition without radiation exposure, which allows for repeated measurements, MRI has functional imaging capacities, for example, assessment of ventilation, perfusion, or diffusion.

Fourier decomposition (FD)-MRI has been demonstrated to deliver quantitative measurement of pulmonary ventilation without use of any contrast media, inhaled gases, or forced breathing maneuvers. Lately, a 2D postprocessing approach, phase-resolved functional lung imaging (PREFUL), was introduced in order to increase temporal resolution and gain quantitative regional information about perfusion and ventilation dynamics. One limitation of the above-mentioned methods with real-time acquisition is low spatial resolution, for example, in comparison to hyperpolarized gas MRI, which can cause discrepancies of derived ventilation parameters between these methods. High spatial resolution is required to facilitate early and accurate diagnosis and to visualize small but clinically relevant pathologies as in CF patients. Alternatively to PREFUL and other real-time acquisition FD techniques, 2D self-gated noncontrast-enhanced functional lung imaging has been introduced to obtain images of the complete respiratory and cardiac cycle with high spatial resolution up to $1.76 \times 1.76$ mm$^2$ with 10 mm thick slices. The main limitation of 2D techniques are through-plane motion and the acquisition of 2D slices, which is time-consuming if the coverage of the whole lung volume is required. Therefore, in most studies, despite the possibility of missing important pathologies, the acquisition is limited to only a few 2D slices. 3D self-navigated approaches were previously developed to enable the acquisition of lung volumes at different breathing states without the necessity for breath-holds and to allow for quantification of lung ventilation; however, no functional information of lung ventilation dynamics has been assessed. In analogy to spirometry, the most common pulmonary function test, ventilation dynamics could be analyzed using flow-volume loops (FVL). FVL derived by 2D PREFUL were found to be sensitive for the detection of early chronic lung allograft dysfunction stages, and the feasibility of 3D MRI-based spirometry using regional lung deformation was demonstrated in a single healthy volunteer.

Also, for the assessment of dynamic ventilation parameters, the temporal resolution of the acquired images might be of interest. For this purpose, different time-resolved measurements (different number of reconstructed breathing phases) with different measurement times should be investigated.

In this study, our objectives were to 1) demonstrate the feasibility of 3D FVL analysis using PREFUL ventilation measurement with improved spatial resolution; 2) compare 3D PREFUL measurement to 2D PREFUL measurement in healthy volunteers and patients with asthma, CF, and COPD; and 3) determine the temporal resolution, which is required to deliver stable ventilation parameters using 3D PREFUL.

2 METHODS

2.1 Subject demographics

Eight healthy volunteers (2 female, 6 male; age range: 28-34 years), 5 asthma patients (4 female, 1 male; age range: 27-70 years), 2 patients with diagnosed CF (1 female, 1 male; both 27 years old), and 1 COPD patient (male, 70 years old) underwent imaging on a 1.5T MR-scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) in head-first supine position. The study was approved by the local ethics committee, and written informed consent was obtained from all participants prior to MRI examination.

2.2 Spirometry

In all patients, a spirometry was performed before MRI examination to measure forced vital capacity (FVC), forced expiratory volume in 1 s (FEV$_1$), and the Tiffeneau index (FEV$_1$/FVC) according to current guidelines.

2.3 Image acquisition

2.3.1 3D PREFUL

For the 3D approach, 6768 to 8184 spokes were acquired using a prototype stack-of-stars spoiled-gradient-echo sequence with golden-angle increment over a period of 9.85 to 12.45 min during free breathing with the following parameters: FOV $50 \times 50$ cm$^2$, matrix size $128 \times 128$ interpolated to $256 \times 256$, slice thickness 4 mm— interpolated to 2 mm, 48-72 partitions, 6/8 partial Fourier applied along the slice dimension, TE 0.81 ms, TR 1.9 ms, flip angle 3.5°, and pixel...
bandwidth 1500 Hz/pixel. To reduce the minimal TE, the prototype stack-of-stars spoiled-gradient-echo sequence uses a hard RF pulse for nonslice selective excitation. Full radial projections are used to sample the k-space so that firstly the samples in $k_p$ partition direction are acquired and followed by the rotation of golden angle to sample the $k_y$-$k_z$ plane.

Similarly to Block et al., system-dependent gradient delays were retrospectively compensated by estimating the k-space shift from the 36 preparation shots acquired at 18 opposing directions with an increment of $10^\circ$. A Hanning filter was applied both in plane and across partitions on gradient delay-corrected datasets to avoid Gibbs ringing.

Low-resolution images (matrix size $32 \times 32$) with a nominal temporal resolution of less than 100 ms were reconstructed for a single dorsal coronal slice posterior to the heart. For each time-point, 14 spokes were required, which resulted in effective temporal resolution of 890 to 1333 ms. Mean signal intensity inside a region of interest placed on the diaphragm in the reconstructed images defined the respiratory curve for all slices. To exclude signal variations, which were not caused by respiration, a low-pass filter at 0.7 Hz was applied to the respiratory curve. After exclusion of extreme outliers of the respiratory curve (data above 95th and data below 10th percentile), spokes were divided into inspiration and expiration phase using the slope of the extracted respiratory curve and a model function with individual breathing frequency. Based on the respiratory curve, data were binned in respiratory phases. At least 100 spokes per respiratory bin were required, which resulted in 53 to 65 respiratory phases. The same number of spokes per respiratory phase was also used in the reconstruction procedure of the 4-min and 8-min PREFUL measurements, which resulted in different numbers of breathing phases ($\approx 20$ phases for 4-min, $\approx 40$ phases for 8-min, and $\approx 60$ phases for 12-min PREFUL measurement). To increase the SNR of the reconstructed images, an overlap of 20% between neighboring respiratory states was used. Finally, the reconstruction of the full-resolution images was implemented in Berkeley Advanced Reconstruction Toolbox using parallel imaging and iterative compressed sensing reconstruction. The sparsity was exploited along both spatial (L2 norm and total variation regularization) and respiratory state dimensions (total variation regularization). The image reconstruction time is approximately 1 h for the whole 3D respiratory-resolved dataset, with 65 respiratory phases using the CPU (2 x Intel Xeon Platinum 8176 @ 2.10GHz, in total 56 physical cores).

The reconstructed images were bias-corrected using N4 Bias Field Correction implemented in Advanced Normalization Tools; bias results from inhomogeneous coil intensity profiles.

The 3D image registration of all respiratory phases toward an end-inspiratory respiratory state was performed by Advanced Normalization Tools using a group-oriented approach.

After registration, 32 breathing phases at an equidistant time grid were interpolated using a Gaussian kernel (sigma = 0.3). A low-pass filter with a cutoff frequency of 0.7 Hz was applied in order to suppress signal variations, which were not attributed to respiration. A 3D edge-preserving filter was applied to all images to smooth away noise while retaining edges. A schematic overview of the data processing of 3D PREFUL is shown in Figure 1.

### 2.3.2 2D PREFUL

For 2D PREFUL, 4 to 14 coronal slices of the lung with 250 images per slice were acquired using a spoiled-gradient-echo sequence with the following parameters: TE 0.82 ms, TR 3 ms, flip angle 5°, FOV 50 $\times$ 50 cm$^2$, slice thickness 15 mm, matrix size $128 \times 128$ interpolated to 256 $\times$ 256, pixel bandwidth 1500 Hz/pixel, and total acquisition time 48 s per slice.

Further postprocessing steps were applied as described elsewhere, with 2 exceptions: 1) the image registration was performed toward end-inspiratory state, and 2) 32 (instead of 60) breathing phases covering the whole respiratory cycle were interpolated.

### 2.4 Image analysis

#### 2.4.1 Slice thickness alignment and coregistration of 3D PREFUL to 2D PREFUL

To enable voxel-wise comparability of 3D and 2D PREFUL measurements of the same patient, the 4 mm 3D PREFUL slices were reformatted to 15 mm slice thickness and then coregistered to 2D PREFUL slices. Datasets of 3D PREFUL, which were reformatted and coregistered, are abbreviated as 3D$_{lowres}$ PREFUL.

#### 2.4.2 Lung parenchyma segmentation

For image analysis, the lung parenchyma was automatically segmented using a pretrained convolutional neural network with 16 weight layers developed by visual geometry group (VGG), which was adapted for lung parenchyma segmentation. If needed, manual corrections were performed to obtain optimal segmentation results.

### 2.4.3 Ventilation assessment of 2D and 3D$_{lowres}$ PREFUL and 3D PREFUL

Because the image registration was performed toward inspiration, regional ventilation (RVent) maps were computed for each respiratory state $N$ as follows:

\[
RVent(N) = \frac{S_{Ref}}{S_{Imp}} - \frac{S_{Ref}}{S_N} = 1 - \frac{S_{Imp}}{S_N},
\]

(1)
where $S_{\text{Ref}} = S_{\text{Insp}}$ and represents MR signal of the end-inspiratory state, and $S_N$ is the MR signal of the $N$-th state.

RVent dynamics were further analyzed by calculation of the regional RVent slopes ($\Delta \text{RVent}/\Delta t$). By plotting the RVent slopes as a function of RVent, a FVL was calculated for each voxel in the lung parenchyma. Similarity of all FVLs to a healthy-reference FVL of each subject was measured by the cross-correlation (CC) metric. The healthy-reference FVL was obtained by averaging the FVLs in a selected region with high RVent values (75%-95% quantile). Thus, a quantitative correlation map of FVL in percent was generated for 2D, 3D lowres PREFUL, and 3D PREFUL measurements.

Moreover, ventilation defect percentage (VDP) maps were generated for RVent (VDP$_{\text{RVent}}$) and CC (VDP$_{\text{CC}}$) parameters using an individual threshold. For VDP$_{\text{RVent}}$, voxels were identified as ventilation defect if the RVent value was below the 90th percentile of all RVent values, multiplied by a factor of 0.4, based on area under curve analysis of previously acquired 2D PREFUL data. For VDP$_{\text{CC}}$, voxels with CC values below 0.9 were considered as voxels with ventilation defect.

### Stability of 3D PREFUL

To assess the stability of RVent dynamics, ventilation time-to-peak (VTTP) maps in % of the synthesized respiratory cycle were reconstructed. The synthesized respiratory cycle is normalized to the duration of 1 breath, starts at a peak expiration, and is symmetrical about the peak inspiration at 50%. Based on mentioned definitions, a healthy VTTP is located at 50% of the synthesized respiratory cycle (see Supporting Information Figure S1). Furthermore, the deviation of each VTTP value (VTTP$_{\text{Dev}}$) from the peak at 50% was evaluated, as follows:

$$\text{VTTP}_{\text{Dev}} = |\text{VTTP} - 50\%|.$$

The analysis of VTTP$_{\text{Dev}}$ was performed on healthy volunteers only because it was expected that in healthy subjects the heterogeneity of VTTP values should be very low, ideally equal to 0%.

Lung ventilation parameters were further examined regarding the required temporal resolution. For this purpose, all ventilation parameters (RVent, CC, VTTP$_{\text{Dev}}$, VDP$_{\text{RVent}}$, VDP$_{\text{CC}}$) derived from 4-min, 8-min, and 12-min measurements, respectively, were assessed separately.

### 2.5 Statistical analysis

All statistical analyses were performed in MatLab (R2018b, MathWorks, Natick, MA). All data were tested for normality using the Lilliefors test. Nonparametric tests were chosen because none of the parameters showed normal distribution.
PREFUL-derived ventilation parameters (median RVent, median CC, total VDP_{RVent}, total VDP_{CC}) were correlated with spirometry-derived ventilation parameters (FVC, FEV₁, FEV₁/FVC) using Pearson correlation in all patients.

Unpaired nonparametric Wilcoxon rank sum test was used to compare diseased patients (asthma, CF, COPD) versus healthy volunteers for the medians of demographic and ventilation-based parameters, including age, body mass index and RVent, CC, VDP_{RVent}, and VDP_{CC} derived by 2D/3D_{lowres}/3D PREFUL measurements.

2D PREFUL-, 3D_{lowres} PREFUL-, and 3D PREFUL-derived ventilation parameters (RVent, CC, VDP_{RVent}, VDP_{CC}) were recorded as median (25th percentile-75th percentile) and assessed using Bland-Altman plots between all pairs. The measure of linear correlation for all ventilation parameters between all pairs was rated by Pearson correlation analysis (r). To test for systematic differences between all pairs, a nonparametric Wilcoxon signed-rank test was used. Bonferroni correction for multiple comparisons (n = 3) was applied so that the significance level of 0.05 was corrected to 0.0167. RVent, CC, VDP_{RVent}, and VDP_{CC} of all diseased patients were tested for correlation with FEV₁, FVC, and FEV₁/FVC. Furthermore, Sørensen-Dice coefficients were evaluated for VDP_{RVent} and VDP_{CC} to compare the spatial overlap for all relevant group pairs.

Also, for the comparison of 3D PREFUL with 3 different measurement times, the median (25th percentile-75th percentile) of ventilation-based parameters (RVent, CC, VTTP_{Dev}, VDP_{RVent}, VDP_{CC}) were computed for all 3D PREFUL measurements (4-min, 8-min, 12-min). The agreement of RVent, CC, VDP_{RVent}, and VDP_{CC} was compared using Bland-Altman plots between 4-min versus 12-min measurements, between 8-min versus 12-min measurements, and between 4-min versus 8-min 3D PREFUL measurements. Linear correlation of derived ventilation parameters (RVent, CC, VTTP_{Dev}, VDP_{RVent}, VDP_{CC}) was assessed using Pearson correlation analysis (r) between 4-min versus 12-min measurements, between 8-min versus 12-min measurements, and between 4-min versus 8-min 3D PREFUL measurements. Statistical significance of the median RVent, CC, VTTP_{Dev}, VDP_{RVent}, and VDP_{CC} of above-mentioned groups was tested using a nonparametric Friedman test and post hoc multi comparison analysis with significance level of 0.05. The regional agreement of VPD maps (4-min vs. 12-min, 8-min vs. 12-min, 4-min vs. 8-min) was assessed by Sørensen-Dice coefficients. Additionally, distributions of RVent and CC values between 4-min versus 12-min measurements, 8-min versus 12-min measurements, and 4-min versus 8-min measurements were evaluated by means of histogram analysis; spatial overlap of distributions in % was calculated.

### 3 RESULTS

#### 3.1 Comparison of healthy volunteers and patients with lung disease

Table 1 presents demographic and spirometry- and ventilation-based parameters derived by 2D, 3D_{lowres}, and 3D PREFUL.

Compared to the healthy volunteer group, VDP_{RVent} and VDP_{CC} were significantly higher (all P < .01) in patients with chronic lung disease for 2D PREFUL, 3D_{lowres} PREFUL, and 3D PREFUL. For all techniques, healthy volunteers showed a higher CC metric value in comparison to patients (all P < .001). Significant correlations (all P < .032) between spirometry parameters and 2D/3D_{lowres}/3D PREFUL-derived ventilation parameters were found, except the correlation of FVC and FEV₁/FVC with RVent parameter derived by 2D PREFUL and the correlation of FVC with RVent parameter derived by 3D_{lowres} PREFUL (see Supporting Information Table S1).

#### 3.2 Comparison of 2D, 3D_{lowres} and 3D PREFUL

Visual comparison of 2D, 3D_{lowres}, and 3D PREFUL-derived ventilation parameter maps is shown in Figures 2 and 3 for a healthy volunteer and an asthma patient, respectively. Although a high similarity of VDP_{RVent} and VDP_{CC} (mean difference = −2%, P = .0004) decreased for 3D PREFUL with VDP_{CC} (mean difference = −6%, P = .0004) were significantly increased for 3D PREFUL, and CC metric (mean difference = 0.02, P = .0004) decreased for 3D PREFUL with high resolution. Complete results are listed in Table 2 for all
study participants and in Supporting Information Table S2 for patients and healthy volunteers separately. See Supporting Information Figure S6 for exemplary 3D PREFUL-derived parameters for a healthy volunteer (33 years), asthma patient (70 years, FEV1 = 63%), CF patient (27 years, FEV1 = 85%), and COPD patient (70 years, GOLD IV, FEV1 = 18%). Full respiratory cycles with spatial resolution interpolated to 2 × 2 × 2 mm³, derived by 3D PREFUL, may be seen in Supporting Information Videos S1-S3 for a CF patient (27 years, FEV1 = 79%)/healthy volunteer (33 years)/asthma patient (57 years, FEV1 = 71%).

### 3.3 Comparison of 4-min, 8-min, and 12-min 3D PREFUL

Supporting Information Figures S2 and S3 show functional 3D PREFUL RVent maps for a healthy volunteer/an asthma patient acquired in 12 min. RVent, CC, VDP_{RVent}, and VDP_{CC} of 3D PREFUL were not significantly different between the 4-min versus 12-min measurements, 8-min versus 12-min measurements, and 4-min versus 8-min measurements, except for the CC metric, which was significantly higher for 8-min in comparison to 4-min PREFUL measurement (P = 0.0218), also confirmed in the Bland-Altman analysis (see Supporting Information Figures S4 and S5). High positive linear relationship of all parameters was observed using the Pearson correlation analysis (r = 0.51-0.99) (see Table 3) between 4-min versus 12-min measurements, 8-min versus 12-min measurements, and 4-min versus 8-min measurements. See Figure 6 for a visual comparison of the VDP_{RVent} maps of a COPD patient derived in 4 and 12 min 3D PREFUL measurement, respectively. Median Sørensen-Dice coefficients between VDP maps of RVent and CC were higher than 0.81 and increased absolutely with the measurement time by approximately 4% and 6% for VDP_{RVent} and VDP_{CC}, respectively (see Supporting Information Table S3). In a similar fashion, the histogram analysis of RVent and CC showed high spatial overlap of the distributions between 3D PREFUL measurements (>86.4%). Absolute median increase in spatial overlap of 7.7% and 0.2% for RVent and CC was seen.

### Table 1 Demographic, spirometric data, and ventilation-based parameters from 2D PREFUL, 3D_{lowres} PREFUL and 3D PREFUL

| Method        | Parameter          | All (n = 16) | Normal (n = 8) | Patients (n = 8) | P Values**  | Normal vs. Diseased Patients |
|---------------|--------------------|--------------|----------------|------------------|-------------|----------------------------|
| Age [years]   | 33.0 [28.8-56.3]   | 31.0 [28.8-33.0] | 56.50 [42.8-63.3] | x              | 0.10        |
| Male/female   | 9/7                | 6/2          | 3/5            | x                |             |
| BMI [kg/m²]   | 23.2 [20.8-26.6]   | 22.2 [21.3-26.0] | 24.3 [19.9-28.2] | 0.96          |
| FVC [% pred]  | x                  | x            | 80.0 [77.5-90.5] | x                |             |
| FEV₁ [% pred] | x                  | x            | 67.0 [58.0-73.0] | x                |             |
| FEV₁/FVC [%]  | x                  | x            | 66.0 [57.8-68.0] | x                |             |
| 2D PREFUL     | RVent [mL/mL]      | 0.13 [0.11-0.18] | 0.14 [0.11-0.17] | 0.13 [0.11-0.18] | 0.96        |
|               | CC [-]             | 0.95 [0.90-0.97] | 0.97 [0.96-0.98] | 0.88 [0.74-0.93] | 0.0011      |
|               | VDP_{RVent} [%]    | 10.1 [7.5-24.0] | 6.9 [5.1-8.5]   | 24.1 [12.5-37.8] | 0.0011      |
|               | VDP_{CC} [%]       | 12.4 [6.4-20.0] | 6.3 [4.8-7.2]   | 20.0 [13.9-37.4] | 0.0006      |
| 3D_{lowres} PREFUL | RVent [mL/mL] | 0.12 [0.11-0.13] | 0.12 [0.11-0.13] | 0.12 [0.11-0.13] | 0.96        |
|               | CC [-]             | 0.97 [0.93-0.98] | 0.98 [0.97-0.98] | 0.92 [0.88-0.97] | 0.0047      |
|               | VDP_{RVent} [%]    | 8.7 [6.2-15.0]  | 6.2 [4.4-7.3]   | 14.0 [9.4-26.7]  | 0.0104      |
|               | VDP_{CC} [%]       | 5.4 [2.2-22.0]  | 1.9 [0.86-4.0]  | 22.5 [12.2-30.7] | 0.003       |
| 3D PREFUL     | RVent [mL/mL]      | 0.15 [0.14-0.16] | 0.15 [0.14-0.17] | 0.15 [0.14-0.16] | 0.44        |
|               | CC [-]             | 0.94 [0.90-0.96] | 0.96 [0.96-0.97] | 0.89 [0.84-0.94] | 0.003       |
|               | VDP_{RVent} [%]    | 10.9 [6.6-18.4] | 6.5 [5.1-8.7]   | 18.3 [12.4-29.5] | 0.007       |
|               | VDP_{CC} [%]       | 13.6 [5.3-28.6] | 5.1 [3.3-8.4]   | 31.1 [18.7-41.7] | 0.0019      |

Values are expressed as median [25th-75th percentile] for demographic data and ventilation-based parameters. P < .05 was considered significant (marked in red).

3D_{lowres}, low-resolution 3D PREFUL; BMI, body mass index; CC, cross-correlation metric; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PREFUL, phase-resolved functional lung; RVent, regional ventilation; VDP_{CC}, ventilation defect percentage based on CC; VDP_{RVent}, ventilation defect percentage based on RVent.

*Wilcoxon rank sum test.
(see Supporting Information Table S3) when the measurement time was doubled. The heterogeneity of VTTPDev values of the 12-min measurement was significantly decreased ($P < .0076$) in comparison to the 4-min measurement (see Figure 7). A similar trend, however, not statistically significant ($P < .06$), was seen in the comparison of 8-min measurement and 4-min measurement. These findings suggest a more stable measurement performed in 8 and 12 min.

4 | DISCUSSION

The main finding of this work is that the novel 3D PREFUL technique was able to deliver dynamic information about lung ventilation with very good agreement to the conventional 2D PREFUL approach in 16 study participants: 8 healthy volunteers and 8 patients with chronic pulmonary diseases, including asthma, CF and COPD.

As expected, CC metric derived by all 3 PREFUL techniques was significantly higher in healthy volunteers in comparison to patients with pulmonary disease. Conversely, VDP$_{RVent}$ and VDP$_{CC}$ were significantly lower for healthy volunteers. These findings are in agreement with previously published results. No significant differences were found for RVent between healthy volunteers and patients. As discussed previously, tidal volume might be controlled or used for adjustment of regional ventilation values for a reasonable comparison of RVent between healthy volunteers and diseased patients. Also, as described previously in a study in CF patients, relatively healthy parenchyma may compensate for more diseased parenchyma so that the mean RVent measurement of the whole lung volume does not change between normal controls and patients.

Further, we observed that all ventilation parameters derived by 3D PREFUL including RVent, CC, VDP$_{RVent}$ and VDP$_{CC}$ correlate strongly with spirometric measurements in all patients. Similar results were found also for 3D$_{lowres}$ except for correlation between RVent and FVC, which was not found significant. Significant correlations were found also between 2D PREFUL-derived ventilation parameters and spirometric data, except for the correlation of RVent.
FIGURE 3  Comparison of 2D, 3D<sub>lowres</sub>, and 3D PREFUL-derived parameters for an asthma patient (70 years, FEV<sub>1</sub> = 63%). From top to bottom, the rows show the RVent and CC maps, FVL as averages of areas with CC > 0.9 (blue), CC < 0.9 (red), reference healthy (green), all areas (black), and VDP<sub>RVent</sub> and VDP<sub>CC</sub> maps. Similar pattern of defect areas in RVent, CC, and VDP maps may be seen for all techniques. FEV<sub>1</sub>, forced expiratory volume in 1 s

FIGURE 4  Bland-Altman analysis between RVent and CC derived with 2D, 3D<sub>lowres</sub>, and 3D PREFUL. First row, RVent comparisons; second row, CC comparisons. First column, 2D versus 3D<sub>lowres</sub>; second column, 2D versus 3D; third column, 3D<sub>lowres</sub> versus 3D. Please note, different scaling of y-axis in the comparison of CC metric between 3D<sub>lowres</sub> and 3D PREFUL.
parameter with FEV$_1$, FVC, and FEV$_1$/FVC. Similar correlation coefficients were seen previously in patients with asthma, CF, and COPD.$^{9,38,39}$ Significant correlations of 3D PREFUL techniques with RVent parameter may be explained by the fact that the complex breathing motion in the lung parenchyma is likely better captured with a 3D technique than with a 2D technique.

In the present study, we showed good correspondence of 3D PREFUL regional ventilation parameters (RVent, VDP$_{RVent}$) and FVL analysis-derived parameters (CC and VDP$_{CC}$) with the same parameters derived by 2D PREFUL in healthy volunteers and patients. The agreement of the static ventilation parameter RVent between 2D and 3D is in correspondence with previously reported results in 6 healthy volunteers.$^{18}$ The potential of FVL analysis using 2D PREFUL has been demonstrated in 62 lung transplantation recipients.$^{22}$ To our knowledge, 3D PREFUL FVL have never been demonstrated in patients previously, and this is the first study to compare FVL-derived parameters between 2D and 3D technique in healthy volunteers and patients with chronic pulmonary diseases. Small discrepancies, for example, those seen in Figure 2 in the left lung of a healthy volunteer or in Figure 3 for an asthma patient, might be explained by nonperfect match of both segmented mask, imperfect motion correction, different healthy regions taken as healthy reference loop, and different spatial resolution.

Significant differences were observed between 3D$_{lowres}$ versus 3D for all derived parameters and between 3D$_{lowres}$ vs. 2D for FVL-derived parameters. Prominent inconsistencies in comparison of 3D$_{lowres}$ versus 3D-derived parameters are probably consequences of nonperfect spatial averaging in the step of slice alignment of 3D PREFUL datasets to 2D PREFUL datasets. As a result of spatial averaging, the spatial resolution of 3D$_{lowres}$ is decreased; therefore, small ventilation defects may not be detected, which supports our results that both VDP's derived by 3D$_{lowres}$ PREFUL are significantly decreased in comparison to 3D PREFUL-derived VDPs. Thus, 3D PREFUL is likely to be more sensitive to detect regions of hypoventilation and heterogeneity of ventilation in patients, which is beneficial for early detection and improved monitoring in chronic lung disease patients. Although good agreement of all ventilation parameters ($r > 0.67$, Dice coefficient of VDP$_{RVent}$ and VDP$_{CC} > 0.84$) was found between 2D and 3D$_{lowres}$, several reasons might explain the pronounced differences in the comparison of FVL analysis-derived parameters (CC and VDP$_{CC}$). Aside from the imperfect coregistration of 2D/3D slices and different regions taken as reference loops for FVL analysis, the through-plane lung motion is expected to be better captured with the 3D technique. As a consequence, the shape of FVL is different (see Figures 2 and 3), which resulted in the disagreement between FVL-derived parameters.

3D PREFUL-derived ventilation parameters acquired in 4, 8, and 12 min were not significantly changed, except for the CC metric between the 4-min and 8-min measurements and the VTT$^{PDev}$ parameter between the 4- and 12-min PREFUL measurements. Because the Pearson correlation coefficient $r$ between the 4-min and 8-min 3D PREFUL-derived CC metric was 0.97, and the median spatial overlap was higher than 90%, the explanation for the significantly higher CC metric values for the 8-min measurement in comparison to the 4-min 3D PREFUL measurement may be the increased variability of tidal breathing resulting in

**FIGURE 5** Bland-Altman analysis between VDP$_{RVent}$ and VDP$_{CC}$ derived with 2D, 3D$_{lowres}$, and 3D PREFUL. First row, VDP$_{RVent}$ comparisons; second row, VDP$_{CC}$ comparisons. First column, 2D versus 3D$_{lowres}$; second column, 2D versus 3D; third column, 3D$_{lowres}$ versus 3D.
changes of the breathing pattern. Among others, respiratory drift may cause image quality degradation, as seen in cardiovascular MR imaging. Various gating techniques have been developed to tackle respiratory-induced motion in cardiac MRI. Because we use retrospective gating for sorting of acquired spokes into respiratory bins, which does not account for the respiratory drift, the influence of respiratory drift might not be neglected. The significantly increased VTTP_{Dev} parameter in the 4-min measurement can be explained by the reduced number of reconstructed breathing phases in comparison to 8-min (12-min) PREFUL measurement. Since for every phase the same number of spokes was used in the reconstruction procedure, only the number of breathing phases is different (≈20 phases for 4-min vs. ≈60 phases for 12-min measurement). Thus, the number of reconstructed phases significantly influences the stability of the respiratory cycle such that VTTP heterogeneity of the 4-min measurement is higher in contrast to more stable 8-min and 12-min measurements. Mapping of ventilation phase using 2D PREFUL has been demonstrated previously as an interesting method to visualize abnormal ventilation dynamic. Therefore, longer measurements (>8 min) of 3D PREFUL should be performed in case the VTTP parameter is of interest in the particular study. Otherwise, overall good agreement of other derived ventilation parameter shows that 3D PREFUL is feasible during free breathing even in 4-min scan time, which may be especially advantageous with small children or patients for whom the scan time plays an essential role. Further, if the dynamic ventilation parameters are not of interest in a particular study, the number of respiratory bins may be reduced using more data in each respiratory bin, which will improve the SNR of phase-resolved images.

We acknowledge a number of study limitations: First, the reproducibility of 3D PREFUL was not tested in this study. There are several studies examining the reproducibility of 2D FD-based techniques. Considering the very good agreement between 2D and 3D PREFUL, the reproducibility of 3D PREFUL-derived parameters can be expected to be at least as good because the motion of the lung is fully captured and additional variability between different slice positions is avoided.

Second, validation of 3D PREFUL to clinically established ventilation measurements (SPECT/CT) or gas MRI imaging techniques (^{129}Xe, ^{3}He, ^{19}F) has not been performed in this work and needs to be investigated in future studies with larger number of patients and a broader spectrum of disease severity. In the last years, 2D FD-derived techniques with partial coverage of the lung parenchyma were validated to SPECT and gas MRI techniques, with partial success due to lower spatial resolution and missing full lung coverage with 2D FD techniques.
Third, the sample size was relatively small, and there was no age-matching between healthy volunteers and patients. Nevertheless, we do not expect that the limited sample size substantially changes the conclusions of this exploratory study.

Fourth, in comparison to 3D UTE/zero echo time (ZTE) or 3D bSSFP pulmonary imaging, the used prototype stack-of-stars pulse sequence with golden angle increment possesses a longer TE and therefore achieves in general reduced SNR and resolution with the above-mentioned techniques. Supporting Information Figure S7 shows comparison of morphological images for a healthy volunteer using a prototype stack-of-stars sequence with asymmetric readout (TE = 0.39 ms) and the proposed stack-of-stars sequence with symmetric readout (TE = 0.81 ms). In contrast to UTE, 3D stack-of-stars trajectory sequence offers faster filling of k-space and is less prone to gradient imperfections.

Fifth, using the nonselective hard RF pulse, the sequence is not able to measure the inflow effect; therefore, perfusion measurement is not feasible with the 3D PREFUL technique.

Further development, including improvement of the spatial resolution, reduction of echo time, applicability on 3T systems, and consideration of the discussed limitations, is of high interest and will be subject to future work.
3D PREFUL ventilation MRI depicts the whole lung volume and complex lung ventilation dynamics with superior image resolution and likely more precision compared to 2D PREFUL. Furthermore, high-resolution 3D PREFUL is more sensitive to detect regions of hypoventilation and ventilation heterogeneity compared to low-resolution 3D lowres PREFUL, which is important for early detection and improved monitoring of patients with chronic lung disease. Also, the measurement time of 3D PREFUL may be reduced up to 8 min, which might be beneficial in clinical settings.

**ACKNOWLEDGMENT**

This work was funded by the German Center for Lung Research (DZL) and open access funding enabled and organized by Projekt DEAL. The authors profited from a number of beneficial discussions with colleagues, in particular with Arnd Obert, Tawfik Moher Alsady, and Christoph Czerner (Hannover Medical School, Department of Radiology). The authors would also like to thank Melanie Pfeifer and Frank Schröder from Department of Radiology (Hannover Medical School) for outstanding technical assistance in performing the MRI examinations.

**CONFLICT OF INTEREST**

Robert Grimm is an employee of Siemens Healthcare GmbH, Erlangen, Germany.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

FIGURE S1 Scheme of 3D PREFUL-derived ventilation time-to-peak map (VTTP). The dotted green curve shows the RVent dynamics over the length of the respiratory cycle in %. VTTP in % of the respiratory cycle is measured from the end-expiration towards the end-inspiration peak

FIGURE S2 Exemplary 3D PREFUL RVent maps with isotropic spatial resolution of $2 \times 2 \times 2 \text{ mm}^3$ for a healthy volunteer (33 years). Please note the depiction and signal of the trachea and bronchial tree details with 3D PREFUL. Also, 3D PREFUL RVent maps show absent signal in the cardiovascular structures with good image sharpness and fine detail

FIGURE S3 Exemplary 3D PREFUL RVent maps with isotropic spatial resolution of $2 \times 2 \times 2 \text{ mm}^3$ for a 70-year-old asthma patient (FEV$_1$ = 63%). Note regional ventilation defects preferably in the lower left lung lobe

FIGURE S4 Bland-Altman analysis between RVent and CC derived with 3D PREFUL in 4, 8 and 12 minutes. First row, RVent comparisons, second row, CC comparisons. First column, 4-minute vs. 12-minute PREFUL; second column, 8-minute vs. 12-minute PREFUL; third column, 4-minute vs 8-minute PREFUL

FIGURE S5 Bland-Altman analysis between VDPR Ventura and VDPCC derived with 3D PREFUL in 4, 8 and 12 minutes. First row, VDPRVenta comparisons, second row, VDPCC Comparisons. First column, 4-minute vs 12-minute PREFUL; second column, 8-minute vs 12-minute PREFUL; third column, 4-minute vs 8-minute PREFUL

FIGURE S6 Exemplary 3D PREFUL-derived parameters for a healthy volunteer (33 years), asthma patient (70 years, FEV$_1$ = 63%), cystic fibrosis patient (years, FEV$_1$ = 85%) and COPD patient (70 years, GOLD IV, FEV$_1$ = 18%). From top to bottom, the rows show the RVent and CC maps, flow volume loops (FVL), VDP RVent and VDP CC maps

FIGURE S7 Representative morphological images for a healthy volunteer using a prototype stack-of-stars sequence with asymmetric readout (first row, TE = 0.39 ms) and chosen stack-of-stars sequence with symmetric readout (second row, TE = 0.81 ms). Red arrows point out lung parenchyma regions with unexpected reduced signal intensity/image artifacts in the images acquired with asymmetric readout

TABLE S1 Correlation of spirometry and 2D, 3Dlowres and 3D PREFUL-derived ventilation parameters for all patients

TABLE S2 Summary of ventilation results obtained by 2D PREFUL, 3Dlowres PREFUL and 3D PREFUL for healthy volunteers (A) and patients (B), and the respective statistical, image analysis

TABLE S3 Image analysis of 3D PREFUL derived ventilation parameters during the 4-minute measurement (4’), 8-minute measurement (8’) and 12-minute measurement (12’) for all study participants

VIDEO S1 Full respiratory cycle of a CF patient (27 years, FEV$_1$ = 79%) displayed in coronal plane with spatial resolution of $2 \times 2 \times 2 \text{ mm}^3$

VIDEO S2 Full respiratory cycle of a healthy volunteer (33 years) displayed in sagittal plane with spatial resolution of $2 \times 2 \times 2 \text{ mm}^3$

VIDEO S3 Full respiratory cycle of an asthma patient (57 years, FEV$_1$ = 71%) displayed in axial plane with spatial resolution of $2 \times 2 \times 2 \text{ mm}^3$

How to cite this article: Klimeš F, Voskrebenzev A, Gutberlet M, et al. 3D phase-resolved functional lung ventilation MR imaging in healthy volunteers and patients with chronic pulmonary disease. Magn Reson Med. 2021;85:912–925. https://doi.org/10.1002/mrm.28482