Perfusion quantification using voxel-wise proton density and median signal decay in PREFUL MRI

Julian Glandorf\(^1,2\) | Filip Klimes\(^1,2\) | Lea Behrendt\(^1,2\) | Andreas Voskrebenzev\(^1,2\)
Till F. Kaireit\(^1,2\) | Marcel Gutberlet\(^1,2\) | Frank Wacker\(^1,2\) | Jens Vogel-Claussen\(^1,2\)

\(^1\)Institute for Diagnostic and Interventional Radiology, Hannover Medical School, Hannover, Lower Saxony, Germany
\(^2\)Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Member of the German Centre for Lung Research (DZL), Hannover, Lower Saxony, Germany

Correspondence
Jens Vogel-Claussen, Institute for Diagnostic and Interventional Radiology (OE 8220), Hannover Medical School, 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).

Purpose: Contrast-free lung MRI based on Fourier decomposition is an attractive method to monitor various lung diseases. However, the accuracy of the current perfusion quantification is limited. In this study, a new approach for perfusion quantification based on voxel-wise proton density and median signal decay toward the steady state for Fourier decomposition-based techniques is proposed called \(Q_{\text{Quant}}\) (\(Q_{\text{Quant}}\)).

Methods: Twenty patients with chronic obstructive pulmonary disease and 18 patients with chronic thromboembolic pulmonary hypertension received phase-resolved functional lung-MRI (PREFUL) and dynamic contrast-enhanced (DCE)-MRI. Nine healthy participants received phase-resolved functional lung-MRI only. Median values of \(Q_{\text{Quant}}\) were compared to a Fourier decomposition perfusion quantification presented by Kjørstad et al (\(Q_{\text{Kjørstad}}\)) and validated toward pulmonary blood flow derived by DCE-MRI (\(\text{PBFDCE}\)). Blood fraction maps determined by the new approach were calculated. Regional and global correlation coefficients were calculated, and Bland-Altman plots were created. Histogram analyses of all cohorts were created.

Results: The introduced parameter \(Q_{\text{Quant}}\) showed only 2 mL/min/100 mL mean deviation to \(\text{PBFDCE}\) in the patient cohort and showed less bias than \(Q_{\text{Kjørstad}}\). Significant increases of regional correlation with \(\text{PBFDCE}\) were achieved (\(r = 0.3\) vs. \(r = 0.2, P < .01^*\)). The trend of global correlation toward \(\text{PBFDCE}\) is not uniform, showing higher values for \(Q_{\text{Kjørstad}}\) in the chronic obstructive pulmonary disease cohort than for \(Q_{\text{Quant}}\) and vice versa in the chronic thromboembolic pulmonary hypertension cohort. In contrast to \(Q_{\text{Kjørstad}}\), \(Q_{\text{Quant}}\) perfusion maps indicate a physiologic dorsoventral gradient in supine position similar to \(\text{PBFDCE}\) with similar value distribution in the histograms.

Conclusion: We proposed a new approach for perfusion quantification of phase-resolved functional lung measurements. The developed parameter \(Q_{\text{Quant}}\) reveals a higher accuracy compared to \(Q_{\text{Kjørstad}}\).

KEYWORDS
Fourier decomposition, perfusion quantification, PREFUL
Currently, there are various available techniques for quantitative imaging of regional lung perfusion using diverse imaging modalities such as MRI, CT, positron emission tomography CT, and single photon emission CT. Among these modalities, MRI has the potential to be a standard technique for long-term surveillance of chronic lung diseases because it involves no ionizing radiation combined with high spatial resolution.

The different MRI techniques can be further divided into intravenous contrast media-based techniques, for instance, DCE-MRI and dynamic susceptibility contrast MRI, and into contrast-free methods like arterial spin labeling, phase contrast MRI, and techniques related to Fourier decomposition (FD) such as phase-resolved functional lung (PREFUL) MRI.1-5 In particular, the imaging of perfusion is desirable because it is a sensitive parameter for various pathologic processes. It is defined as the mean blood exchange per time per defined organ volume and usually stated with the unit mL/min/100 mL.

DCE-MRI is a well-established method for quantitative MR pulmonary perfusion analysis in healthy and diseased patients.6-8 Its basis is the acquisition of multiple 3D volumes with high temporal resolution using a T1-weighted sequence during the administration of gadolinium-based contrast agents. The resulting signal-time series can either be interpreted by applying tracer-kinetic models or by model-free techniques.7

PREFUL MRI offers the possibility to assess phase-resolved pulmonary perfusion and ventilation without any contrast agent during free breathing. This approach was shown to be feasible with fast imaging sequences such as the steady-state free precession sequence and the widely available and generic spoiled gradient echo sequence FLASH.2,9,10 In image acquisitions of a gradient-echo sequence, multiple RF pulses are delivered within short time intervals. By this, the longitudinal magnetization is not able to recover completely between the upcoming pulse repetitions and the signal decreases to a steady state level. At this constant signal level, the regain of longitudinal magnetization equals the amount of transverse magnetization evoked by the next RF pulse. The static spins are being saturated. During each heartbeat, unsaturated blood spins enter the imaging plane and lead to a flow-related signal enhancement. Consequently, in a voxel with high perfusion more saturated spins are being replaced by unsaturated spins between systole and diastole leading to a higher signal amplitude (Q) compared to a voxel with low perfusion. Perfusion-related signal (Q) is defined as the difference between the signal at tmax and tmin, representing the time with the highest and the lowest signal of the perfusion-weighted time series inside the parenchyma.

Currently, PREFUL perfusion maps are either interpreted as perfusion-weighted information with arbitrary units11 or the values are quantified in mL/min/100 mL using the Kjørstad method (QKjørstad).12-14

The basis of this method is the normalization of the perfusion-related signal (Q) to a signal amplitude in a pure blood voxel during the steady state (S0Aorta). T is the time between two heartbeats (see Equation 1).12 During the recent years, several studies validated perfusion-weighted parameters derived by FD-MRI techniques to DCE-MRI.11,15-17

However, a major limitation of this method is the variability of the signal within the lumen of the aorta. It depends on flow velocity varying from 1 m/s in healthy subjects up to > 4 m/s in patients with severe aortic valve stenosis. Furthermore, the degree of turbulence and the angle of flow within the imaging plane have an impact on the signal.18,19 Thus, a novel approach for perfusion quantification tackling this major drawback is of interest.

1.1 | Theory

The introduced parameter QQuantified (QQuant) is based on exchange fraction and blood fraction, which are defined in the following and in Table 1.

1.2 | Exchange fraction

A pure blood voxel with a minimal level of saturation would exert the maximum available magnetization before the first excitation at t = 0. We define the median difference in the parenchyma region of interest between the signal at t = 0 (S0par) and the median steady-state signal (S1par) as Delta S. By comparing the signal amplitude Q to Delta S, the exchange fraction of each voxel can be estimated: exchange fraction = Q/(S0par − S1par). This is the proportion of mobile spins being exchanged during every heartbeat (Figure 1).

1.3 | Blood fraction

The blood fraction is approximated because we assume that the vast amount of signal is originated in blood. For this, the voxel-wise signal of the parenchyma voxel at t = 0 (S0par) is divided by the signal of a vessel voxel at t = 0 (S0ves). Blood fraction = S0par/S0ves. In contrast to the method of Kjørstad,12 blood fraction is determined at the beginning of the sequence to avoid flow effects. Consequently, S0par and
S0ves are estimated by extrapolating the first 4 samples by a monoexponential fit (Figure 2).

Furthermore, the signal at the beginning of the sequence is highly dependent on the current respiratory state. To compensate this, a correction factor is determined during the steady state by comparing the signal of the mid-respiratory position to the signal of the same diaphragm position during the sequence start. This correction factor is then applied to estimate S0par in mid-respiratory state.

Exchange fraction, blood fraction, and the time between two heartbeats (T) can be further used to quantify perfusion:

\[
Q_{\text{Quant}} = \text{exchange fraction} \times \text{blood fraction} \times \frac{1}{T} \times \frac{100}{2 \times \text{voxel volume}}
\]

(2)

\[
Q_{\text{Quant}} = \frac{Q}{(S0par - S1par \#)} \times \frac{S0par}{S0ves \#} \times \frac{1}{T} \times \frac{100}{2}.
\]

(3)

The voxel volume is cancelled out. Values indicated with \# are determined globally for the whole imaging slice.

**Abbreviation**: ROI, region of interest.

### METHODS

#### 2.1 | Participants

In this retrospective analysis, data sets of 38 patients consisting of 20 patients with chronic obstructive pulmonary disease (COPD) and 18 patients with chronic thromboembolic pulmonary hypertension (CTEPH) were postprocessed and analyzed retrospectively. Inclusion criteria were as follows: COPD patients ≥ 40 years with stable cardiovascular function, a smoking history of ≥ 10 years, and a clinical COPD diagnosis were included. CTEPH patients ≥ 18 years with suspected pulmonary hypertension in transthoracic echocardiography were included. Additionally, 9 healthy participants were evaluated. Participants with contraindications to undergo MRI (e.g., pregnancy, pacemaker) were excluded. Further details of inclusion and exclusion criteria have been described previously.22,23

The study was approved by the local ethics committee, and written informed consent was obtained from all study participants.

#### 2.2 | DCE-MRI

Additionally, all patients received DCE-MRI to allow for correlations of PBF\textsubscript{DCE} with the quantified PREFUL values \(Q_{\text{Kjøsstad}}\) and \(Q_{\text{Quant}}\). The DCE examinations were acquired during a single breath-hold at end inspiration using a bolus of 0.033 to 0.04 mmol/kg bodyweight of gadolinium-based contrast agents injected at a rate of 5 mL/s. PBF\textsubscript{DCE} was calculated using a deconvolution algorithm based on the Volterra formula, as described previously by Sourbron et al.\textsuperscript{15,24,25} The patients were examined at 1.5T (Magnetom Avanto, Siemens Healthineers, Erlangen, Germany). The settings used for a 3D time-resolved
angiography with a stochastic trajectories sequence are presented in Table S1 in the Supporting Information section.

2.3 | PREFUL MRI

The participants were examined using a spoiled gradient echo sequence (FLASH) at 1.5 Tesla at the same scanner with the following parameters (Table 2):

Three coronal slices (dorsal, central, and ventral of the carina) were acquired for all participants. Parallel imaging with GRAPPA with acceleration factor 2 was performed. All participants were scanned in head-first supine position during free breathing, and all images were interpolated to the final in-plane resolution of 256 x 256 pixels by zero-filling of k-space data prior to reconstruction. The nonuniform intensity profiles of the applied receiver coils were corrected using the sensitivity profiles of the surface and body coil before PREFUL analysis.

2.3.1 | Image registration

All PREFUL datasets were registered using advanced normalization tools for linear and diffeomorphic image registration with a group-oriented registration scheme to achieve a uniform respiratory position. In contrast to previous described registration schemes, the first 20 images of each sequence were included. Each data set was segmented visually using individual thresholds, followed by manual corrections to include the vast majority of the lung parenchyma and to exclude large central lung vessels.

2.3.2 | Full cardiac cycle reconstruction

A detailed description of the cardiac cycle reconstruction process has been described previously. Briefly, a high pass filter at 0.75 Hz was applied to the registered images in order to exclude signal changes due to respiration. The cardiac phase of each time point was estimated by piecewise fitting the averaged signal of an aorta region of interest to a sine function. Phase information was calculated after sorting...
Perfusion (Q) was calculated by taking the difference between the signal at the time with the highest and the lowest signal of the perfusion weighted time series in the segmented parenchyma region of interest. In addition to the introduced new $Q_{Quant}$, perfusion was quantified according to Kjørstad et al.\textsuperscript{12} The signal $S_{0par}$ and $S_{0ves}$ were determined prior to filtering and are corrected to the mid-respiratory level. ROI, region of interest.

**TABLE 2** Sequence parameters of PREFUL MRI

| Parameters            | COPD       | CTEPH     | Healthy  |
|-----------------------|------------|-----------|----------|
| Sequence              | FLASH      | FLASH     | FLASH    |
| FOV [mm$^2$]          | 500 × 500  | 440 × 440 | 500 × 500 |
| Matrix size           | 128 × 96   | 128 × 96  | 128 × 128 |
| Slice thickness [mm]  | 15         | 15        | 15       |
| TE [ms]               | 0.82       | 0.67-0.89 | 0.82     |
| TR [ms]               | 3          | 3         | 3        |
| Flip angle [$^\circ$] | 5          | 5-8       | 5        |
| Pixel bandwidth [Hz/pixel] | 1500      | 1085-1502 | 1500    |
| Acceleration factor   | 2          | 2         | 2        |
| Images per slice      | 200        | 200       | 250      |
| Number of slices      | 3          | 3         | 3        |

Abbreviations: COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; PREFUL MRI, phase-resolved functional lung MRI.
high pass filter. An exponential fit was used to extrapolate the first four signal points to t = 0. A correction factor was used to adapt the values to the mid-respiratory state assuming a linear dependency of signal and diaphragm position described by Zapke.28

2.4 Comparison of PREFUL-MRI and DCE-MRI

Due to a different slice thickness, a compound coronal DCE slice corresponding to the PREFUL image was calculated. For this, DCE slices were multiplied by a normalized slice-overlap weighting factor and summed up according to the position and overlap toward the PREFUL images.29 PREFUL- and DCE-MRI images were then coregistered to achieve voxel-wise comparability.

2.5 Statistics

MatLab R2018a (MathWorks, Natick, MA) and JMP Pro 14 (SAS Institute, Cary, NC) were used for the statistical analysis. The Shapiro-Wilk test revealed no normal distribution of all parameters in the pretest. Correlations after Bravais and Pearson and Bland-Altman plots between $Q\text{Quant}$, $Q\text{Kjørstad}$, and DCE were calculated. Differences of the central tendency were evaluated using a Wilcoxon signed-rank test. Histogram analyses were created for all cohorts. Results with $P \leq .05$ were considered significant.

3 RESULTS

3.1 Patient characteristics

A total number of 47 participants consisting of 20 patients with COPD, 18 patients with CTEPH, and 9 healthy individuals were included. The median age of the COPD cohort was 66 years, of the CTEPH cohort was 62 years, and of the healthy cohort was 33 years. In particular, the COPD group revealed an unequal gender distribution with a female proportion of 15%. The proportion of females in the CTEPH cohort was 44%, and the female proportion in the healthy cohort was 67%. The overall median age was 60 years, and the overall female proportion was 36%.

3.2 Median quantified perfusion and blood fraction

The median values of both PREFUL quantifications and $PBF_{DCE}$ derived by the DCE are displayed in Table 3. The median values of $PBF_{DCE}$ range from 24 to 30 mL/min/100 mL, of $Q\text{Quant}$ range from 18 to 48 mL/min/100 mL, and of $Q\text{Kjørstad}$ range from 51 to 155 ml/min/100 mL. Both PREFUL quantification methods indicate lower median perfusion for patients with CTEPH compared to COPD patients, whereas the opposite effect can be seen for the $PBF_{DCE}$. In contrast to $Q\text{Kjørstad}$, $Q\text{Quant}$ perfusion maps and blood fraction maps indicate a dorsoventral gradient in supine position similar to $PBF_{DCE}$ (Table 3). Both PREFUL quantification methods show many low and 0 values in the patient cohorts, especially in the CTEPH cohort. The value distribution shows highest similarity between $Q\text{Quant}$ and $PBF_{DCE}$ (Figure 3). Exemplary perfusion-weighted maps, quantified perfusion maps, and blood fraction maps of a COPD and a CTEPH patient are depicted in Figures 4 and 5.

3.3 Regional and global correlation

Voxel-wise correlations between $Q\text{Quant}$ and $Q\text{Kjørstad}$ show very high Pearson coefficients, with median values between $r = 0.90$ and $r = 0.95$, $P < .01$. Median voxel-wise correlations between PREFUL quantifications and $PBF_{DCE}$ are noticeably lower, ranging between $r = 0.18$ and $r = 0.33$, $P < .01$. However, significant increases of the voxel-wise
correlations toward $\text{PBF}_{\text{DCE}}$ were achieved with $Q_{\text{Quant}}$ (correlation $Q_{\text{Quant}}$ to $\text{PBF}_{\text{DCE}}$ vs. correlation $Q_{\text{Kjørstad}}$ to $\text{PBF}_{\text{DCE}}$, $P < .01$). The global correlation with $\text{PBF}_{\text{DCE}}$ was stronger in the COPD cohort ($r > 0.63$, $P < .01$ vs. $r < 0.36$, $P > .15$). In the COPD cohort, $Q_{\text{Kjørstad}}$ delivered a stronger global correlation than $Q_{\text{Quant}}$ ($r = 0.73$, $P < .01$ vs. $r = 0.63$, $P > .01$). In the CTEPH cohort, the global correlation of $Q_{\text{Quant}}$ was stronger than of $Q_{\text{Kjørstad}}$ ($r = 0.36$, $P > .15$ vs. $r = 0.29$, $P > .25$) (Table 4).

3.4 | Bland-Altman plots

Bland-Altman analysis revealed no systematic difference comparing $Q_{\text{Quant}}$ with $\text{PBF}_{\text{DCE}}$ (mean difference = 2 mL/min/100 mL, lower and upper limits of agreement = −36 and 40 mL/min/100 mL). $Q_{\text{Kjørstad}}$ showed marked higher values compared to $\text{PBF}_{\text{DCE}}$ with high SD (mean difference = 64 mL/min/100 mL, lower and upper limits of agreement = −17 and 144 mL/min/100 mL) in all cohorts. Furthermore, visually, a tendency toward increasing differences for extreme mean values of perfusion can be detected for $Q_{\text{Kjørstad}}$ (Figure 6).

4 | DISCUSSION

In this study, we introduced a new approach for perfusion quantification of FD-derived methods using PREFUL as a specific example. The differences to $Q_{\text{Kjørstad}}$ are the separation of blood fraction and flow effects. Flow effects are normalized by utilizing the median signal decay toward the steady state as a reference to calculate the exchange fraction and the blood fraction in calculated prior to reaching steady state to avoid influences of blood flow. The developed parameter $Q_{\text{Quant}}$ reveals smaller differences to $\text{PBF}_{\text{DCE}}$ and lower SD, whereas perfusion is mostly overestimated by the method of Kjørstad. Furthermore, small but significant increases of voxel-wise correlations with $\text{PBF}_{\text{DCE}}$ were achieved. Additionally, blood fraction maps were presented.

The results of lower PBF values in COPD than in CTEPH and vice versa in both PREFUL quantifications may reflect the differing capabilities of DCE- and PREFUL-MRI based
FD methods are genuinely sensitive to changes of the perfusion phase and amplitude. CTEPH typically presents with web stenoses in the conducting pulmonary arteries. Distal of the stenotic web, only a relatively small pulmonary blood volume flows through a highly compliant and low pressure distal pulmonary arterial and capillary vascular bed, leading to a marked decrease in pulse wave velocity. This leads to a phase shift compared to nonobstructed lung segments. Because the presented perfusion quantification method only takes into account the phase in the cardiac cycle with the maximum flow signal in the healthy lung parenchyma, the flow in the (partially) obstructed segments may not be adequately depicted compared to DCE measurements. Furthermore, FD methods may not measure perfusion under a certain level accurately due to their dependency to depict the frequency of the pulsatile parenchymal blood flow. Because the amplitude of the pulse wave distal to a web stenosis may be smaller, it may be more challenging to depict it using FD methods. Taken together, this may cause incongruence between DCE and PREFUL measurements, especially in CTEPH patients.
A potential correction to the phase shift in CTEPH patients could be achieved by the phase selection algorithm described previously by Behrendt et al.29 Another improvement could be the calculation of the area under the curve (AUC) of the perfusion signal instead of its amplitude similarly to DCE-MRI.34 Moreover, DCE inherits various inaccuracies regarding different deconvolution models,7 noise, imperfect measurement of arterial input function due to relatively low temporal resolution, and in pathologies like emphysema due to marginal signal.35 However, additional parameters such as the capillary permeability or the blood volume can currently only be determined from DCE data on the basis of a tracer-kinetic model.7 Regarding the limited validity of DCE-MRI, especially in diseased lung tissue, future studies comparing the PREFUL quantification to lung perfusion single photon emission CT and investigating its reproducibility and the exact height of perfusion would strengthen its value. Patient positioning could also be switched to prone position to invert the physiological gradient in future studies. Nevertheless, a real gold standard has not been developed yet.

Another important limitation is the influence of lung segmentation on the correlation coefficients. Fully automated segmentation would reduce variability. Additionally, variations of signal occur in FD-based methods by the use of different sequences and scan parameters.9,10,36 Further inaccuracies result by varying respiratory states at the beginning of each sequence that might only be roughly anticipated by the used correction factor.

Of course, the proposed blood fraction is a simple approximation of spin density within the lung tissue. Nevertheless, assuming a 2-compartment model, no differentiation between extravascular and intravascular lung water is determined. The more of extravascular lung water exists (eg, due to edema or infiltrate), the more overestimation occurs. More sophisticated approaches deliver higher blood volume fractions and would increase the perfusion results, if applied to our formula.37,38 Furthermore, the ratio between extravascular voxel fraction and intravascular voxel fraction changes in pathology leading to less calculated blood fraction in fibrosis and higher calculated blood fraction in edema or infiltrate. This would lower perfusion results of fibrosis and increase results within edema or infiltrates. Nevertheless, our simple approach visualizes a ventro-dorsal gradient and leads to comparable perfusion values as DCE-MRI. The missing gradient in the PBF-DCE data might be due to a relatively short slice gap between the 3 slices. The opposite gradient of Q_Kjørstad might be explained by the absence of a large vessel determining “vessel signal.” Because small arteries have smaller differences of blood flow, the resulting small vessel signal as the denominator in the Q_Kjørstad formula leads to high perfusion values in the ventral slice.

The use of a median value of Delta S for the quantification of a whole parenchyma slice does not reflect inhomogeneities in lungs with advanced pulmonary diseases. Ideally, Delta S should be determined for each voxel, but this led to artifacts

| TABLE 4 | Regional voxel-wise and summed global correlation with PBF_DCE |
|---------|---------------------------------|-----------------|
|         | Regional correlation to PBF_DCE | Global correlation to PBF_DCE |
|         | Dorsal | Central | Ventral | Dorsal | Central | Ventral |
| COPD    |        |         |         |        |         |         |
| Q_{Quant} | 0.32   | 0.33    | 0.21    | 0.63   |         |         |
|         | P < .01* | P < .01* | P < .01* | P < .01* |         |         |
| Q_{Kjørstad} | 0.29   | 0.28    | 0.19    | 0.73   |         |         |
|         | P < .01* | P < .01* | P < .01* | P < .01* |         |         |
| CTEPH   |        |         |         |        |         |         |
| Q_{Quant} | 0.30   | 0.27    | 0.33    | 0.36   |         |         |
|         | P < .01* | P < .01* | P < .01* | P = .15 |         |         |
| Q_{Kjørstad} | 0.23   | 0.18    | 0.28    | 0.29   |         |         |
|         | P < .01* | P < .01* | P < .01* | P = .25 |         |         |
| Wilcoxon signed-rank test: Correlation Q_{Quant} to PBF_DCE vs. Correlation Q_{Kjørstad} to PBF_DCE |
| P < .01* | P < .01* | P < .01* |

Comparison of the regional correlations using a Wilcoxon signed-rank test. Values marked with * are considered as significant.
in emphysematous regions of COPD patients, yielding only minimal signal decay (results not shown here) and inaccu-
acies of the registration process. More accurate fitting of the signal decay could be achieved by the use of retrospective

gating either by an electrocardiogram or by a self-gated MR sequence.4

Nevertheless, compared to DCE-MRI, the FD-based methods are completely noninvasive and do not require long breath-holds, which makes it attractive for clinical settings.

5 | CONCLUSION

We proposed a new approach for perfusion quantification of PREFUL measurements. The developed parameter reveals smaller differences to the established DCE-MRI and a similar value distribution. Significant increases of voxel-wise correlations toward PBFDCE were achieved.

ACKNOWLEDGMENT

This work was funded by the German Center for Lung Research (DZL). The authors would like to express their gratitude to the medical technical assistants Frank Schröder and Melanie Pfeifer from the Department of Radiology for their support with the MR measurements and patient care.

ORCID

Julian Glandorf https://orcid.org/0000-0003-1927-9876
Filip Klimeš https://orcid.org/0000-0003-2715-0757
Andreas Voskrebenzev https://orcid.org/0000-0001-5699-1841
Jens Vogel-Claussen https://orcid.org/0000-0001-5595-6948

REFERENCES

1. Hopkins SR, Wielpütz MO, Kauczor HU. Imaging lung perfusion. J Appl Physiol. 2012;113:328-339.
2. Bauman G, Puderbach M, Deimling M, et al. Non-contrast-enhanced perfusion and ventilation assessment of the human lung by means of Fourier decomposition in proton MRI. Magn Reson Med. 2009;62:656-664.
3. Voskrebenzev A, Gutherlet M, Klimeš F, et al. Feasibility of quantitative regional ventilation and perfusion mapping with phase-resolved functional lung (PREFUL) MRI in healthy volunteers and COPD, CTEPH, and CF patients. Magn Reson Med. 2018;79:2306-2314.
4. Fischer A, Weick S, Ritter CO, et al. SElf-gated non-contrast-enhanced functional lung imaging (SENCEFUL) using a quasi-random fast low-angle shot (FLASH) sequence and proton MRI. NMR Biomed. 2014;27:907-917.
Bolar DS, Levin DL, Hopkins SR, et al. Quantification of regional pulmonary blood flow using ASL-FAIRER. *Magn Reson Med.* 2006;55:1308-1317.

Jackson A, Buckley DL, Parker GJM. *Contrast-Enhanced Magnetic Resonance Imaging in Oncology.* Jackson A, Buckley DL, Parker GJM, eds. Berlin, Heidelberg: Springer; 2005.

Sourbron SP, Buckley DL. Classic models for dynamic contrast-enhanced MRI. *NMR Biomed.* 2013;26:1004-1027.

Sourbron S, Luyraert P, Morhard D, Seeces K, Reiser M, Peller M. Deconvolution of bolus-tracking data: a comparison of discretization methods. *Phys Med Biol.* 2007;52:6761-6778.

Rotärmel A, Voskrebzenz A, Klimes F, Guterlet M, Wacker F, Vogel J. GRE hSSFP vs. FLASH based Fourier decomposition lung MRI at 1.5T: evaluation of image quality, fractional ventilation and lung perfusion in healthy volunteers. In Proceedings of the 26th Annual Meeting of ISMRM, Paris, France, 2018, p. 2-4.

Bauman G, Pusterla O, Bieri O. Functional lung imaging with transient spoiled gradient echo. *Magn Reson Med.* 2019;81:1915-1923.

Kaireit TF, Voskrebzenz A, Guterlet M, et al. Comparison of quantitative regional perfusion-weighted phase resolved functional lung (PREFUL) MRI with dynamic gadolinium-enhanced regional pulmonary perfusion MRI in COPD patients. *J Magn Reson Imaging.* 2019;49:1122-1132.

Kjøstad Å, Corteville DMR, Fischer A, et al. Quantitative lung perfusion evaluation using Fourier decomposition perfusion MRI. *Magn Reson Med.* 2014;72:558-562.

Kjøstad Å, Corteville DMR, Hentzer T, Schmid-Bindert G, Zöllner FG, Schad LR. Non-invasive quantitative pulmonary V/Q imaging using Fourier decomposition MRI at 1.5T. *Z Med Phys.* 2015;25:326-332.

Bauman G, Bieri O. Matrix pencil decomposition of time-resolved proton MRI for robust and improved assessment of pulmonary ventilation and perfusion. *Magn Reson Med.* 2017;77:336-342.

Behrendt L, Voskrebzenz A, Klimes F, et al. Validation of automated perfusion-weighted phase-resolved functional lung (PREFUL)-MRI in patients with pulmonary diseases. *J Magn Reson Imaging.* 2020;52:103-114.

Bauman G, Scholz A, Rivoire J, et al. Lung ventilation- and perfusion-weighted Fourier decomposition magnetic resonance imaging: in vivo validation with hyperpolarized 3He and dynamic contrast-enhanced MRI. *Magn Reson Med.* 2013;69:229-237.

Bauman G, Puderbach M, Heimann T, et al. Validation of Fourier decomposition MRI with dynamiccontrast-enhanced MRI using visual and automatically scored of pulmonary perfusion in young cystic fibrosis patients. *Eur J Radiol.* 2013;82:2371-2377.

Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr.* 2009;10:1-25.

Otto CM. Aortic stenosis—listen to the patient, look at the valve. *N Engl J Med.* 2000;343:652-654.

Fischer A, Pracht ED, Arnold JFT, Kotas M, Flentje M, Jakob PM. Assessment of pulmonary perfusion in a single shot using SEEPAGE. *J Magn Reson Imaging.* 2008;27:63-70.

Pracht ED, Fischer A, Arnold JFT, Kotas M, Flentje M, Jakob PM. Single-shot quantitative perfusion imaging of the human lung. *Magn Reson Med.* 2006;56:1347-1351.

Hohlfeld JM, Vogel-Claussen J, Biller H, et al. Effect of lung deflation with indacaterol plus glycopyrronium on ventilatory filling in patients with hyperinflation and COPD (CLAIM): a double-blind, randomised, crossover, placebo-controlled, single-centre trial. *Lancet Respir Med.* 2018;6:368-378.

Schoenfeld C, Cebotari S, Hinrichs J, et al. MR imaging-derived regional pulmonary parenchymal perfusion and cardiac function for monitoring patients with chronic thromboembolic pulmonary hypertension before and after pulmonary endarterectomy. *Radiology.* 2016;279:925-934.

Sourbron S, Dujardin M, Makkat S, Luyraert P. Pixel-by-pixel deconvolution of bolus-tracking data: optimization and implementation. *Phys Med Biol.* 2007;52:429-447.

Winther HB, Guterlet M, Hundt C, et al. Deep semantic lung segmentation for tracking potential pulmonary perfusion biomarkers in chronic obstructive pulmonary disease (COPD): the multi-ethnic study of atherosclerosis COPD study. *J Magn Reson Imaging.* 2020;51:571-579.

Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage.* 2011;54:2033-2044.

Voskrebzenz A, Guterlet M, Kaireit TF, Wacker F, Vogel-Claussen J. Low-pass imaging of dynamic acquisitions (LIDA) with a group-oriented registration (GOREG) for proton MR imaging of lung ventilation. *Magn Reson Med.* 2017;78:1496-1505.

Zapke M, Topf H-G, Zenker M, et al. Magnetic resonance lung function—a breakthrough for lung imaging and functional assessment? A phantom study and clinical trial. *Respir Res.* 2006;7:106.

Behrendt L, Voskrebzenz A, Klimes F, et al. Validation of automated perfusion-weighted phase-resolved functional lung (PREFUL)-MRI in patients with pulmonary diseases. *J Magn Reson Imaging.* 2020;52:103-114.

Olsson KM, Meyer B, Hinrichs J, Vogel-Claussen J, Hoepfer MM, Cebotari S. Chronic thromboembolic pulmonary hypertension. *Dtsch Arztebl Int.* 2014;111:856-862.

Pauwels RA, Buist AS, Calverly PM, Jenkins CR, Hud SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;163:1256-1276.

Motley HL, Cournand A, Werko L, Himmelstein A, Dresdale D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am J Physiol Content.* 1947;150:315-320.

Vogel-Claussen J, Schönfeld C-O, Kaireit TF, et al. Effect of indacaterol/glycopyrronium on pulmonary perfusion and ventilation in hyperinflated patients with chronic obstructive pulmonary disease (CLAIM) a double-blind, randomized, crossover trial. *Am J Respir Crit Care Med.* 2019;199:1086-1096.

Sourbron S, Ingrisch M, Siefert A, Reiser M, Herrmann K. Quantification of cerebral blood flow, cerebral blood volume, and blood-brain-barrier leakage with DCE-MRI. *Magn Reson Med.* 2009;62:205-217.
SUPPORTING INFORMATION
Additional Supporting Information may be found online in the Supporting Information section.

TABLE S1 Sequence parameters of DCE-MRI

How to cite this article: Glandorf J, Klimeš F, Behrendt L, et al. Perfusion quantification using voxel-wise proton density and median signal decay in PREFUL MRI. Magn Reson Med. 2021;86:1482–1493. https://doi.org/10.1002/mrm.28787