1336

1H-guided reconstruction of 19F gas MRI in COPD patients

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Purpose: To reduce acquisition time and improve image quality and robustness of ventilation assessment in a single breath-hold using 1H-guided reconstruction of fluorinated gas (19F) MRI.

Methods: Reconstructions constraining total variation in the image domain, L1 norm in the wavelet domain, and directional total variation between 19F and 1H images were compared in order to accelerate 19F ventilation imaging using retrospectively undersampled data from a healthy volunteer. Using the optimal constrained reconstruction in 8 patients with chronic obstructive pulmonary disease (16-seconds breath-hold), ventilation maps of various acceleration factors (2-fold to 13-fold) were compared with maps of the full data set using the Dice coefficient, difference in volume defect percentage and overlap percentage, as well as hyperpolarized 129Xe gas MRI.

Results: The reconstruction constraining total variation and directional total variation simultaneously performed best in the healthy volunteer (RMS error = 0.07, structural similarity index = 0.77) for a measurement time of 2 seconds. Using the same reconstruction in the patients with chronic obstructive pulmonary disease, the Dice coefficient of defect volumes was 0.86 ± 0.05, the mean difference in volume defect percentage was −1.0 ± 1.7 percentage points, and the overlap percentage was 87% ± 2% for a measurement time of 6 seconds. Between volume defect percentage of 19F and 129Xe, a linear correlation (r = 0.75; P = .03) was found, with 19F volume defect percentage being significantly higher (mean difference = 11%; P = .04).

Conclusion: 1H-guided reconstruction of pulmonary 19F gas MRI enables reduction of acquisition time while maintaining image quality and robustness of functional parameters.

KEYWORDS
1H-guided reconstruction, 19F, perfluoropropane, pulmonary MRI, ventilation
1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is among the most frequent causes of death with more than 3 million deaths per year.¹ Lung function testing is the clinical standard for diagnosis and severity assessment of COPD. However, it provides no regional information of the lung and fails to identify different phenotypes of the disease. Alternatively, CT or nuclear medical techniques (eg, single proton emission CT [SPECT]) may be used to assess regional structural and functional information of the lung. However, the exposure to ionizing radiation limits their application.

Magnetic resonance imaging is evolving as an alternative method to gain regional pulmonary information without any harmful radiation. Structural proton lung MRI provides morphological information of the lung parenchyma, airways, and vessels.²⁻⁴ Furthermore, a direct measurement of ventilation is feasible using inhaled-gas MRI. Unrivaled image quality is achieved using hyperpolarized ¹²⁹Xe MRI, which is capable of measuring biomarkers such as ventilation defect percentage (VDP),⁵ ADC,⁶ alveolar wall thickness, and gas uptake into blood.⁷

Magnetic resonance imaging of fluorinated gases may provide a low-cost alternative to hyperpolarized noble gas MRI.⁸,⁹ Due to its large gyromagnetic ratio and the rapid signal recovery, fluorinated gas (¹⁹F) imaging is feasible at thermal polarization. Fluorinated gases (eg, SF₆, C₂F₆, C₃F₈ [perfluoropropane], C₄F₈) are nontoxic, chemically inert, and can be inhaled over several minutes in a mixture with oxygen.¹⁰,¹¹ Consequently, not only static ventilation and diffusion imaging,¹² but also the measurement of functional pulmonary parameters such as gas wash-in and wash-out dynamics,¹³ the low SNR especially after only one breath of gas is a major limiting factor for clinical translation of ¹⁹F MRI. This becomes even more challenging in patients with severely limited breath-holding capacity, in order to keep MRI scan times at a minimum for patient comfort.

So far, ¹⁹F gas MRI has been optimized for SNR requiring the use of antibiotic treatment within the last 3 months. From June 2018 to April 2019, 8 patients with COPD underwent ¹⁹F gas MRI in a guided reconstruction to further decrease the acquisition time of ¹⁹F gas MRI while maintaining image quality and robustness of functional pulmonary parameters in patients with COPD.

2 | METHODS

2.1 | Study population

This prospective study was approved by the local ethics committee. All subjects provided written informed consent prior to examination. Patients with COPD of different severity (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages II and III) were included in this study. Exclusion criteria were inability to undergo MRI (eg, MR-incompatible pacemaker, claustrophobia), pregnancy, age younger than 18 years, and COPD exacerbation requiring the use of antibiotic treatment within the last 3 months. From June 2018 to April 2019, 8 patients with COPD were scanned for this study (7 males, mean age: 65.8 ± 9.2 years, 4 with GOLD stage II, 4 with GOLD stage III). Additionally, 1 healthy endurance athlete was examined in February 2019 (male, 28 years). Detailed information on all scanned subjects is provided in Table 1. On the same day, all patients with COPD underwent ¹¹H, ¹⁹F, and hyperpolarized ³He MRI.

2.2 | Magnetic resonance imaging

Imaging was performed on a 1.5T MR scanner (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) with a transmit Helmholtz birdcage coil and a
16-channel phased-array receive coil (Rapid Biomedical, Rimpar, Germany) both tuned to 59.9 MHz. High-resolution $^1$H (HR $^1$H) MRI was performed in a single breath-hold using the $^{19}$F receive coil tuned to the $^1$H frequency (63.3 MHz).

After inhalation of pure oxygen for 3 minutes, each study participant inhaled a mixture of 79% $C_3F_8$ and 21% oxygen using closed facemask tubing from a reservoir bag as previously described. The subjects took two breaths (the first breath to primarily inhale the remaining oxygen in the delivery tubing) followed by $^{19}$F MRI in one inspiratory breath-hold. $^{19}$F imaging was performed using a prototype 3D gradient-echo sequence with golden-angle stack-of-stars k-space encoding. To capture the current position of the diaphragm for motion correction of different breath-holds, a low-resolution $^1$H image was acquired for 3.9 seconds within the same breath-hold. The breath-hold for patients with COPD took approximately 16 seconds, and for the healthy volunteer 132 seconds.

$^{129}$Xe MRI was performed on the same MR system using a dedicated transmit Helmholtz birdcage coil and a 16-channel phased-array receive coil (Rapid Biomedical, Rimpar, Germany) both tuned to 17.6 MHz. The patients inhaled a gas mixture containing 500-600 mL isotopically enriched $^{129}$Xe, 400-500 mL nitrogen, and a variable amount of air to achieve a total volume of one-third of the subject’s forced vital capacity. In breath-hold, $^{129}$Xe MRI was performed using a prototype balanced SSFP sequence with stack-of-stars readout. For segmentation of the thoracic cavity, $^1$H images were acquired in a separate breath-hold after inhalation of an equal volume of air using a spoiled gradient-echo sequence.

Detailed information on the imaging parameters is provided in Table 2.

Throughout the whole imaging session, the pulse rate, oxygen saturation level, expiratory carbon dioxide level, and breathing frequency were monitored by a physician.

### Image reconstruction

#### $^1$H

$^1$H images were reconstructed using the inline reconstruction on the scanner using CAIPIRINHA (Controlled Aliasing In Parallel Imaging Results IN Higher Acceleration) reconstruction for high-resolution images, and GRAPPA reconstruction for low-resolution images. The HR $^1$H images were co-registered offline to the low-resolution $^1$H images using Advanced Normalization Tools.

#### $^{19}$F

$^{19}$F images of the healthy volunteer were reconstructed using the parallel imaging and compressed-sensing algorithm of the Berkeley Advanced Reconstruction Toolbox. While the full data set (number of excitations \(NEX = 10, 208\) spokes) was reconstructed using nonuniform fast Fourier transform (NUFFT), subsequently undersampled datasets\((NEX=2, n^*8\) spokes) were regularized using

- L1 norm of the image in the wavelet domain
- total variation in the image domain (TV)
- directional TV between the $^{19}$F and the registered HR $^1$H image domain (dTV)
- directional TV and TV regularization applied simultaneously (dTV + TV)

For noise reduction, all undersampled data sets were additionally regularized using the L2 norm in the image domain.

Although $^1$H and $^{19}$F images of the lung show completely different information, both images comprise a similar structure due to the same underlying anatomy. Thus, the gradient

### Table 1

| COPD patient | Age (years) | Sex | BMI (kg/m²) | FEV1 (% predicted) | GOLD stage | SNR (NUFFT reconstruction) |
|--------------|-------------|-----|-------------|--------------------|------------|---------------------------|
| 1            | 53          | M   | 22.8        | 56                 | II         | 6.03 ± 7.60               |
| 2            | 60          | M   | 27.5        | 43                 | III        | 3.86 ± 1.81               |
| 3            | 77          | M   | 26.8        | 76                 | II         | 3.08 ± 1.03               |
| 4            | 60          | F   | 26.0        | 68                 | II         | 2.49 ± 0.44               |
| 5            | 80          | M   | 26.8        | 61                 | II         | 3.45 ± 1.61               |
| 6            | 55          | M   | 27.1        | 30                 | III        | 4.22 ± 2.41               |
| 7            | 68          | M   | 25.1        | 48                 | III        | 4.86 ± 3.08               |
| 8            | 73          | M   | 24.9        | 49                 | III        | 3.68 ± 1.71               |
| Mean ± SD   | 65.75 ± 10.22 | —   | 25.88 ± 1.55 | 55.13 ± 16.30 | —         | 3.96 ± 1.10               |
| Healthy volunteer | 28 | M   | 21.3        | 105                | —          | 14.53 ± 8.84               |

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in 1 second; and GOLD, Global Initiative for Chronic Obstructive Lung Disease.
images of both modalities are very likely to be similar. To incorporate the information of the location and the direction of edges from one image \( v \) (in this case the \( 1H \) image) into the reconstruction of another image \( u \) (the \( 19F \) image), Ehrhardt et al extended the definition of TV and defined the so-called dTV as

\[
dTV(u) := \sum_{n=1}^{N} \left| P_{\xi_n} \nabla u_n \right|
\]

with \( P_{\xi_n} = x - \langle \xi_n, x \rangle \xi_n \) and the normalized vector-field \( \xi_n := \nabla u_n / [V_v u_n] \) representing the structure of \( v \).32 Given this definition, dTV is minimal for \( u \) being parallel to \( v \) throughout the whole image. Furthermore, if no structural information is given for a certain space, the formulation of dTV reduces to the standard TV, avoiding the generation of false edges.32

Figure 1 shows a schematic representation of the reconstruction method with exemplary images from \( 1H \) and \( 19F \) scans and the respective normalized vector fields showing the structure in the images.

The Berkeley Advanced Reconstruction Toolbox was embedded into code provided by Ehrhardt to combine dTV regularization and the parallel imaging and compressed-sensing algorithm.

Regularization parameters for all regularization types were varied logarithmically (0.001, 0.01, 0.1, 1) for each undersampling factor. Parameters minimizing the RMS error (RMSE) to a reference image from the full data set were used as optimal parameters for the given case.

\( 19F \) images of the 8 patients with COPD were reconstructed using only the dTV + TV regularization and the respective set of optimal regularization parameters. In addition to the full data sets (NEX = 6, 32 spokes), retrospectively undersampled data sets (NEX = 2, 4, and 6; 16, 24, and 32 spokes) were reconstructed to determine whether a higher number of spokes or NEX is more rewarding in very short breath-holds.

### 2.3.3 | \( 129Xe \)

\( 129Xe \) ventilation images were reconstructed similarly using the parallel imaging and compressed-sensing algorithm with L2 regularization. Relative coil sensitivities were estimated from the fully sampled center of k-space and gross \( B_1 \) field inhomogeneity corrected for in the combined images using N4 bias field correction.33

### 2.4 | Image analysis

#### 2.4.1 | Image quality calculation

To assess the quality of \( 19F \) images of the healthy volunteer, images from undersampled data sets were compared with images from the full data set (ground truth) using the RMSE and the structural similarity index (SSIM).44 These two metrics provide consistent results.
2.4.2 Ventilation defect percentage

After a $B_1$ field correction using N4ITK, the registered HR $^1$H image was segmented with seeded region growing to obtain the thoracic cavity volume. The $^{19}$F images were also corrected for $B_1$ field inhomogeneity and masked using the thoracic cavity mask. The image was cut off at the 99th percentile, rescaled from 0 to 1, and then divided into four classes depending on the signal intensity: defect (0.0-0.2), low (0.2-0.4), medium (0.4-0.8), and high intensity (0.8-1.0). Ventilation defect percentage is defined as the ratio between the lung defect volume (signal intensity 0.0-0.2) and the whole lung volume. Ventilation defect percentage was calculated for both $^{19}$F and $^{129}$Xe MRI equivalently.

In the patients with COPD, the Sørensen–Dice similarity coefficient (Dice coefficient) was used to compare ventilated and nonventilated volumes of full and undersampled data sets. Additionally, the overall overlap percentage of defects and ventilated volumes was calculated as well as the absolute difference of VDP for full and undersampled data sets.
2.4.3 | Signal-to-noise ratio

For the patients with COPD and the reference image from the healthy volunteer, the SNR was calculated using Kellman’s method for image reconstruction in SNR units.\(^{47}\) The noise covariance was calculated from noise-only data acquired after the gas washout. The SNR maps were reconstructed using NUFFT and optimum B\(_1\)-weighted combination of the receive array.\(^{48}\)

To separate the signal from the noisy background for the calculation of mean SNR, only voxels with an SNR greater than 2 were taken into account.

2.4.4 | Statistical analysis

The VDP of \(^{19}\)F and \(^{129}\)Xe gas MRI was compared using Bland-Altman plot analysis. In addition, the Pearson correlation coefficient between the two methods was calculated. Significance of the correlation was tested by using the Student’s \(t\)-test distribution of the transformed correlation coefficient.

The Shapiro-Wilk test showed a normal distribution of differences between \(^{19}\)F and \(^{129}\)Xe VDP (\(P = .24\)). Thus, a paired \(t\)-test was used to test for significant differences between \(^{129}\)Xe and \(^{19}\)F VDP. All hypotheses were tested with a significance level of 5%. Values are displayed as mean ± SD for all patients with COPD.

3 | RESULTS

All imaging procedures and maneuvers were well tolerated, and no adverse events were reported. Table 1 lists the demographic characteristics and pulmonary imaging parameters for the 8 patients with COPD and the healthy volunteer.

3.1 | Image quality in healthy volunteer

The RMSE and SSIM measured in the healthy volunteer are shown in Figure 2. Comparing the RMSE and SSIM for different regularization metrics in \(^{19}\)F imaging, at very highly accelerated scans of 2-4 seconds of measurement time, the combination of TV and dTV regularization significantly outperforms the other regularization techniques (such as with a RMSE of 0.07 and an SSIM of 0.77 for 2 seconds of measurement time [acceleration factor of 13 compared with Nyquist sampling]). For short measurement times of less than 5 seconds (acceleration factor of 5), TV and dTV performed similarly. The L1 norm of the image in the wavelet domain regularization performed the worst. For measuring times longer than 6 seconds (acceleration factor of 4), the RMSE and SSIM were becoming increasingly similar for the different regularization methods. A good trade-off may be reached at a scan time of 4-6 seconds using the combination of TV and dTV, at which time the RMSE and SSIM are almost converged. The mean SNR for the reference image reconstructed from the full data set with NUFFT was 14.5 ± 8.8.

Exemplary images reconstructed with different optimized regularizations and their difference to the reference image are shown in Figure 3.

3.2 | Robustness of functional parameters in patients with COPD

Dice coefficients, differences in VDP, and the overlap percentages for defects and ventilated volume are shown in Figure 4 for different measurement times depending on the number of averages (NEX = 2, 4, and 6) and the number of spokes (16, 24, and 32 spokes). For a measurement time of 6 seconds

FIGURE 2 Root mean square error (RMSE; A) and structural similarity index (SSIM; B) for fluorinated gas (\(^{19}\)F) MR images from a healthy volunteer. Images were reconstructed regularizing the L1 norm in the wavelet domain (blue), the total variation (TV; red), the dTV (yellow), and TV + dTV (green) and a various number of radial spokes, resulting in the total measurement time shown on the x-axis. The reconstructed images were compared with a reference image acquired in 132 seconds to gain the presented values for RMSE and SSIM. Results are shown only for optimal regularization parameters.
The Dice coefficient of defect volumes was 0.86 ± 0.05, the difference in VDP was −1.0 ± 1.7 percentage points, and the overlap percentage was 87% ± 2%. With a scan time of 6 seconds, the results are very similar to the results obtained with a measurement time of 10 seconds.

The mean SNR for data reconstructed only with NUFFT for all patients was 4.0 ± 1.0. The SNR of all individual patients is given in Table 1.

Exemplary images reconstructed with different data undersampling factors are shown in Figure 5.

A strong linear correlation between $^{19}$F VDP and $^{129}$Xe VDP was found ($r = 0.75$, $P = .032$).

The paired $t$-test showed a significant difference in $^{19}$F VDP and $^{129}$Xe VDP ($P = .039$). The Bland-Altman plot showed a mean bias of 11 percentage points and 95% limits of agreement of ± 22 percentage points. The linear regression and the Bland-Altman plot are shown in Figure 6.

4 | DISCUSSION

In this work, we presented the dTV as an additional regularization parameter in $^1$H-guided image reconstruction of $^{19}$F ventilation MRI in patients with COPD. We have shown that this technique enables a reduction of scan time by a factor of at least 4 compared with Nyquist sampling, while maintaining image quality and robustness of the assessment of the ventilation defect percentage. The presented results suggest the use of a $^1$H-guided reconstruction with combined regularization (dTV + TV) for $^{19}$F MR ventilation imaging in one breath-hold.

In a healthy volunteer, regularization parameters were optimized for undersampled data sets by minimization of the RMSE using a reference image acquired in a 132-second breath-hold. Because constrained reconstructions influence the noise statistics, SNR calculations were only performed for the NUFFT reconstruction, and therefore not used to
optimize the reconstruction. Furthermore, the SNR is highly
dependent on the regularization parameters (eg, smoothing)
and provides no information on image sharpness and actual
similarity to a reference image.

In addition to the ventilation image quality, functional
parameters such as the VDP are relevant for diagnosis
and patient monitoring. The high values of the Dice co-
efficient and overlap percentage as well as the low values
for VDP difference found in comparison to the reference
emphasize the robustness of the presented method and its
potential clinical value in patients with pulmonary disease.
Nonetheless, the choice of scanning parameters affects
the robustness of clinical parameters, as the reduction of
radial spokes results in an underestimation of VDP. This
fact should be taken into account when balancing between
measured spokes and NEX. We suggest scanning at least 4
excitations and 24 spokes for short-winded COPD patients,
resulting in a measurement time of 6 seconds ($^{19}$F) + 4 sec-
onds ($^{3}$H).

The comparison of $^{19}$F VDP with $^{129}$Xe VDP shows their
close correlation but also a significant difference. $^{19}$F VDP
is significantly higher than $^{129}$Xe, which may be attributed to
the difference in diffusivity, as has been shown for hyperpo-
larized $^{3}$He and $^{129}$Xe gas MRI, and the varying breathing
maneuvers used for imaging. Because the experimental setup
for $^{19}$F ventilation imaging is designed for multiple breath-
holds, no fixed breathing volume was predefined, as being
done for $^{129}$Xe ventilation imaging. Furthermore, the lower
SNR and the lower spatial resolution in $^{19}$F imaging may lead
to an underestimation of ventilated volume.

In contrast to previous studies on accelerated $^{19}$F ventila-
tion imaging, this work explicitly addresses the very first
breath-hold, despite its very low SNR. It has been shown that
the VDP computed from the first breath of the fluorinated
gas mixture significantly correlates with the predicted forced
expiratory volume in 1 second and is most sensitive to detect
regional hypoventilation.

Our study has the following limitations. First is the small
number of patients ($n = 8$) examined at only one research
site. However, our results show the advanced possibilities
of the presented method, which should be further investi-
gated in a larger and more heterogeneous patient cohort at
multiple sites. Furthermore, the assessment of the repro-
ducibility of the presented method was not in the scope of
this study.

The choice of regularization and acceleration parame-
ters has to be done with great care. The information gained
from the mostly homogeneous morphologic lung image
may contradict a potentially inhomogeneous ventilation
image. When overregularization occurs, the ventilation
image might be smoothed out, resulting in the loss of small
structures or defects. In this case, the choice of regulariza-
tion parameters was done using a reference from a healthy

![Diagram](https://example.com/diagram.png)

**FIGURE 4** A, Dice coefficients for ventilated and
nonventilated lung volume. B, Difference in ventilation defect
percentage (VDP). C, Overlap percentage for ventilated and
nonventilated lung volume for 8 patients with chronic obstructive
pulmonary disease (COPD). Images were reconstructed by
regularizing TV + dTV, using 2, 4, and 6 excitations as well as
16, 24, and 32 radial spokes, resulting in the total measurement time
shown on the x-axis. The reconstructed images were compared with
a reference image acquired in 12 seconds (NEX = 6, 32 spokes) to
gain the presented values for Dice coefficients, difference in VDP,
and overlap percentage. The solid lines show the mean values and the
shaded areas the SD for 8 patients with COPD.
FIGURE 5  A,C, $^{19}$F ventilation images. E, $^{1}$H high-resolution image. F, $^{129}$Xe ventilation image. B,D,G, Computed VDP maps from 1 patient with COPD (pat. no. 1, pred. forced expiratory volume in 1 second [FEV1] = 56%). Red areas show ventilation defects, deep blue areas show low ventilation, medium blue areas show medium ventilation, and light blue areas show high ventilation. Images in (A) were reconstructed by regularizing the TV. Images in (C) were reconstructed by regularizing $dTV + TV$, using 2 excitations and 16 spokes (left), 4 excitations and 24 spokes (middle), or 6 excitations and 32 spokes (right). F, The $^{129}$Xe image was reconstructed using 1 excitation and 85 spokes. The rightmost map in (D) was used as a reference to calculate Dice coefficients, VDP difference, and overlap percentage (see Figure 3). Note that the $^{19}$F VDP maps show greater defect volumes (red areas) than the $^{129}$Xe VDP map (G).

FIGURE 6  Correlation (A) and Bland-Altman plot (B) showing the comparison of $^{19}$F VDP and $^{129}$Xe VDP. The calculated Pearson correlation coefficient was $r = 0.75$ ($P = .032$). The Bland-Altman plot shows a mean bias of 11 percentage points and 95% limits of agreement of $\pm 22$ percentage points.
volunteer, which may not always be feasible. We recommend using 0.1 as the regularization factor for dTV and 0.01 for TV for breath-holds with a duration of 6 seconds or shorter, which represents a good compromise between image quality and measurement time when prior optimization is not possible.

Furthermore, the registration process from the HR $^1$H image onto the low-resolution $^1$H image is a potential source of error. A poor alignment of the $^{19}$F and the $^1$H image leads to bad regularization conditions and VDP miscalculation in the outer lung.

The possible reduction of measurement time resulting from the use of the presented technique may improve the clinical acceptance of $^{19}$F lung MRI. Patients unable to comply with longer breath-holds can be scanned with reasonable image quality. Furthermore, an increase of spatial resolution is possible, using the available scan time for additional averaging, potentially enabling the detection of smaller ventilation defects. Dynamic imaging in multiple breath-holds and in free breathing may also benefit from the presented method. Low SNR and blurring can be mitigated when using a $^1$H-guided reconstruction.

5 | CONCLUSIONS

$^1$H-guided reconstruction of $^{19}$F MRI of inhaled fluorinated gases allows reduction of scan time while maintaining image quality and robustness of functional pulmonary parameters. This is an important step toward the clinical application of $^{19}$F gas MRI.

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