Investigating short-time diffusion of hyperpolarized $^{129}$Xe in lung air spaces and tissue: A feasibility study in chronic obstructive pulmonary disease patients

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**Purpose:** To investigate the diffusion of hyperpolarized $^{129}$Xe in air spaces at short-time scales for determination of lung surface-to-gas-volume ratio in comparison to results from chemical shift saturation recovery, CT, and established clinical measures.

**Methods:** A pulse sequence for measurement of time-dependent diffusion of $^{129}$Xe in air spaces at short diffusion times was developed. Gas uptake into lung tissue was measured in the same breathhold using chemical shift saturation recovery spectroscopy in the short-time regime. The potential to obtain the surface-to-gas-volume ratio using a first-order and second-order approximation of the short-time expansion of time-dependent diffusion according to Mitra et al$^{11}$ and its diagnostic relevance were tested in a study with 9 chronic obstructive pulmonary disease patients.

**Results:** Surface-to-gas-volume ratios obtained from time-dependent diffusion were correlated with results from chemical shift saturation recovery, $r = 0.840$, $P = .005$ (first-order fits), and $r = 0.923$, $P < .001$ (second-order fits), and from CT results for second-order fits, $r = 0.729$, $P = .026$. Group means ± SD were 75.0 ± 15.5 cm$^{-1}$ (first-order fits) and 122.3 ± 32.8 cm$^{-1}$ (second-order fits) for time-dependent diffusion, 125.9 ± 43.3 cm$^{-1}$ for chemical shift saturation recovery, and 159.5 ± 50.9 cm$^{-1}$ for CT. Surface-to-gas-volume ratios from time-dependent diffusion with first-order fits correlated significantly with carbon monoxide diffusing capacity as percent of prediction, $r = 0.724$, $P = .028$.

**Conclusion:** Time-dependent diffusion measurements of $^{129}$Xe at short-time scales down to ~1 ms are feasible in chronic obstructive pulmonary patients and provide clinically relevant information on lung microstructure.

**KEYWORDS**
CSSR, diffusion, hyperpolarized $^{129}$Xe, surface-to-volume ratio
1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive, potentially fatal, and to date not curable disease. COPD is estimated to affect more than 300 million people worldwide.1 Due to insufficient treatment options, the best way to change patient outcome is thought to be the early detection of the disease.2 From a research perspective, progress in the treatment of COPD has likely been hampered by insufficient phenotyping of COPD as a highly heterogeneous disease.3

Although the presence of COPD is defined and determined clinically by airway obstruction as seen in spirometry, there is significant evidence that the disease begins much earlier and that a significant fraction of the small airways are already damaged even when spirometry detects only mild obstruction.4

CT can depict lung structure with high resolution and also provides functional information; however, it entails substantial doses of ionizing radiation. Methods of nuclear medicine are still widely used for assessment of lung function but have the drawbacks of ionizing radiation and poor spatial resolution.

MRI can provide a wealth of structural and functional information on almost all organs and parts of the body. The lungs, however, have been notoriously difficult to assess using conventional proton MRI. The main reasons are the low proton density and the large number of susceptibility jumps in the lung tissue, leading to a weak and rapidly dephasing MR signal. Respiratory and cardiac motion further complicate MRI of the lung.

MRI of inhaled hyperpolarized gases, in contrast, provides a means for assessment of lung microstructure and function with high sensitivity to disease and without any detrimental effects to the patient.5,6 Hyperpolarized $^{129}$Xe, in particular, offers unique opportunities for studying lung microstructure and function in vivo by virtue of its solubility in body tissues and blood.7 It is thereby predestined both as a sensitive diagnostic and research tool.

Hyperpolarized $^{129}$Xe has been used to measure surface-to-gas volume ($S/V_g$) ratios of porous materials8 as well as lung tissue9 using the chemical shift saturation recovery (CSSR) method. This measurement relies on some assumptions on the material or tissue, namely on the Ostwald coefficient and the diffusivity of xenon within it. Interestingly, it was previously found that the correlation between $S/V_g$ from CSSR with apparent diffusion coefficient (ADC) measurements was rather moderate.10

It was known for a while that time-dependent diffusion measurements in the short-time regime are sensitive to the surface-to-pore-volume ratio, and Mitra et al11 first derived the quantitative relationship. Although the beauty of this theoretical dependence is that no model assumptions must be made on the structure of the object under study, application to actual MR measurements has mostly been hampered by hardware and other restrictions. The potential applicability of this theory to hyperpolarized gas MR diffusion measurements has been studied using computer simulations by Conrad et al.12 It was found that conventional Stejskal–Tanner sequences would probably not be suitable for achieving sufficiently short diffusion times. Motivated by this work, Carl et al13 later proposed a different approach similar to oscillating gradient sequences for achieving lower diffusion times. Using work from Miller et al14 on the theoretical dependence of $S/V_g$ on ADCs, assessment of $S/V_g$ from time-dependent diffusion measurements in a small hyperpolarized gas phantom was presented. The approach proposed in Ref. [13] has the drawback, however, that the diffusion-weighting gradients will create phase errors mostly due to concomitant fields, which are substantial at field strengths of clinical MRI systems and under realistic measurement conditions, thus preventing accurate measurements in vivo.

To compute the $S/V_g$ ratio using the theory of Mitra et al, Ouriadov et al recently proposed determination of virtual ADCs at different diffusion times by varying the $b$ value at a fixed diffusion time in a conventional Stejskal–Tanner sequence.15 In addition, Xie et al16 estimated $S/V_g$ values in COPD patients and healthy volunteers under some assumptions of tissue geometry by a single $^{129}$Xe ADC measurement at a relatively long diffusion time of 3.6 ms. They proposed that the $S/V_g$ estimated from their ADC and CSSR measurements could be used as a new COPD biomarker.

The purpose of this work was to develop a pulse sequence that measures time-dependent diffusion with as low diffusion times as required for measurement of $S/V_g$ in human lungs. The pulse sequence was tested in COPD patients, and the results were compared to those from established short-time CSSR as well as CT measurements and conventional clinical parameters.

2 | THEORY

The diffusion coefficient of a set of particles can generally be defined as [14]

$$D(t) = \frac{\langle (\vec{r}_n(t) - \vec{r}_n(0))^2 \rangle_n}{2dt},$$

(1)

where $\langle . \rangle_n$ denotes the average over all particles; $\vec{r}_n(t)$ is the location of particle $n$ at time point $t$; and $d$ is the dimensionality of the problem. This definition is independent of the NMR measurement. Mitra et al11 derived the theoretical relationship of the so-defined diffusion coefficient for particles diffusing in a general porous medium

$$D(t) = D_0 \left(1 - \frac{4}{3d\sqrt{\pi}} S \sqrt{D_0 t} + BD_0 t + \alpha \left(\sqrt{D_0 t^3}\right)\right),$$

(2)
where $D_0$ is the diffusion coefficient in free space and $B$ contains terms proportional to the curvature of the medium’s surface as well as surface permeability and surface relaxivity. This result indicates that in any porous medium, for very low diffusion times $t$, the diffusion coefficient will approach the diffusion coefficient in free space, which means that most particles did not sense the medium’s boundaries. When increasing diffusion time, a growing fraction of particles will have sensed the boundaries and the diffusion coefficient deviates from free diffusion as $\sqrt{t}$ with a prefactor proportional to $S/V_g$, which is known as the short-time regime (Figure 1). This first-order approximation can be expected to break down if $t$ becomes of the order of $(S/V_g)^{-2}/D_0$; that is, for lower $S/V_g$ ratios as in emphysematous lungs, it should be possible to use longer diffusion times compared to healthy lungs.

Equation (2) is only valid within the narrow pulse approximation of MR diffusion measurements, which has often to be violated in practice because narrow pulses do not produce sufficient diffusion weighting. It has been shown in previous work\cite{14,17,18} that time-dependent ADCs $D_{\text{app}}(\Delta)$ from measurements using wide diffusion-weighting pulses in the low $b$ value limit with approximately Gaussian diffusion exhibit the same short-time behavior as in Equation (2) but with a different prefactor $\alpha$, depending on the shape of the pulses,

$$D_{\text{app}}(\Delta) = D_0 \left(1 - \frac{\alpha}{d \sqrt{S/V_g}} \sqrt{D_0 \Delta} + B' \Delta + o(\sqrt{D_0 \Delta^3})\right),$$

with $\Delta$ the diffusion time of the MR measurement, defined as the separation of the centers of the 2 gradient pulses (Figure 2A). It was found by Carl et al\cite{13} that for repeated sinusoidal pulses as used in our work, $\alpha \approx 0.894$, which agrees well with previous results from numerical simulations and theoretical considerations.\cite{14,18}

3 | METHODS

3.1 | Sequence design

Because the $b$ value of a given diffusion-weighting gradient pulse pair is proportional to the cube of diffusion time for wide pulses, it is very hard to achieve sufficient diffusion weighting at short diffusion times. One way around this problem is the repetition of the diffusion-weighting gradients, which effectively leads to a summation of the $b$ values of each individual gradient pulse pair. This approach is followed in oscillating-gradient sequences; however, straightforward application of oscillating-gradient sequences to hyperpolarized gas diffusion measurements in the lung is hampered by the fact that edge enhancement, as it occurs in the transition from strictly Gaussian diffusion to the localization regime,\cite{19} leads to deviations of the total diffusion-weighting from the product $N b_s D_{\text{app}}(\Delta)$, with $N$ the number and $b_s$ the $b$ value of individual gradient pairs.\cite{13} It was thus suggested to introduce a waiting time between each gradient pulse pair. In order to achieve higher $b$ values, we first adapted the pulse sequence proposed in Ref. [13] by applying the gradients $G$ repetitively using multiple gradient coils simultaneously with the following cycling scheme.

![Image](A.png)

**FIGURE 1** Short-time diffusion in a pore and relevant length scales. (A) Schematic illustrating the concept of diffusion in the short-time regime. In approximation, for diffusion lengths much smaller than pore size $l_0$, only a fraction of spins less than 1 diffusion length $l_D$ away from pore boundaries (hatched area) experience diffusion restriction. The rest of the spins diffuses with the free diffusion coefficient $D_0$. (B) Phase plot for estimation of diffusion regime in which measurements are carried out. From results of first-order fits (white points), a free diffusion of 0.122 cm$^2$/s and an effective pore size of $l_g = 829.6$ µm were assumed. Black points analogously show the estimate for second-order fits assuming a free diffusion of 0.14 cm$^2$/s and $l_g = 530.9$ µm. Although the diffusion length $l_D$ is still the smallest length scale involved, all points lie in the border region between approximately free diffusion ($l_D$ smallest length) and localization regime (dephasing length $l_G = (D_0 G)^{1/3}$ smallest length). Healthy lung tissue is expected to have a reduced effective pore size of ~240 µm based on $S/V_g$ of ~250 cm$^{-1}$.\cite{26} With a diffusion time of 1 ms, one obtains $l_D \approx 120$ µm, suggesting the method should in principle be feasible also in healthy subjects. $S/V_g$, surface-to-gas-volume ratio.
It was proposed in Ref. [13] to divide the signal of the decaying magnetization between diffusion-weighting gradients by the FID signal and fit an exponential function to this ratio to obtain the ADC. Instead, we propose to apply a stack-of-spiral readout after the last diffusion-weighting gradient pulse pair. No dephasing is applied prior to the spiral readout in the central partition of $k$-space such that the $k$-space center does not experience any diffusion weighting due to the spiral imaging gradients. In addition, the spiral readout and 3D encoding gradients are chosen with sufficiently low resolution such that the diffusion weighting of outer regions of $k$-space due to the imaging gradients is small compared to the diffusion weighting of the actual diffusion-weighting pulse pairs. This leads to the sequence diagram for the diffusion-weighted imaging part of the sequence, as depicted in Figure 2A.

\[
\begin{pmatrix}
G_x \\
G_y \\
G_z
\end{pmatrix}
= \begin{pmatrix}
1 & 1 & -1 \\
1 & -1 & \sqrt{2} \\
0 & \sqrt{2} & 0
\end{pmatrix}
\begin{pmatrix}
G_0 \\
G_0 \\
G_0
\end{pmatrix}
\begin{pmatrix}
-\sqrt{2} \\
\sqrt{2} \\
0
\end{pmatrix}
\]  

(4)

It was proposed in Ref. [13] to divide the signal of the decaying magnetization between diffusion-weighting gradients by the FID signal and fit an exponential function to this ratio to obtain the ADC. Instead, we propose to apply a stack-of-spiral readout after the last diffusion-weighting gradient pulse pair. No dephasing is applied prior to the spiral readout in the central partition of $k$-space such that the $k$-space center does not experience any diffusion weighting due to the spiral imaging gradients. In addition, the spiral readout and 3D encoding gradients are chosen with sufficiently low resolution such that the diffusion weighting of outer regions of $k$-space due to the imaging gradients is small compared to the diffusion weighting of the actual diffusion-weighting pulse pairs. This leads to the sequence diagram for the diffusion-weighted imaging part of the sequence, as depicted in Figure 2A.

The following sequence parameters were used: TR/TE 36/21 ms, flip angle 7.4°, FOV 36 cm x 36 cm, matrix size 36 x 36, slice thickness 4 cm, 6 slices, spiral readout with 18 turns, measurement time 36 ms x 11 x 6 ≈ 2.4 s. Ten diffusion weighted acquisitions and 1 unweighted acquisition were obtained. In 1 patient, 10 different diffusion times were measured, whereas in all other patients the lowest diffusion time was repeated at different $b$ values. A fixed waiting time of 2000 µs between the sinusoidal gradient pulse pairs was used for all diffusion times to avoid potential influence from edge enhancement effects. A fixed TE was used for all measurements. Data were acquired in an interleaved manner; that is, for a given $k$-space partition all different diffusion times were measured before the 3D encoding was changed to the next $k$-space partition. See Table 1 for details of parameters used for diffusion-weighting gradients.

A CSSR spectroscopy acquisition without spatial localization was implemented in the same sequence directly after all diffusion-weighted imaging acquisitions. Two 2.4 ms long RF saturation pulses with 200 µs gap were irradiated on the

FIGURE 2 Sequence diagrams. (A) Sequence diagram for diffusion-weighted imaging of $^{129}$Xe in airspaces. A short FID is acquired before diffusion-weighting gradients are played out for normalization purposes, that is, for distinguishing signal decay due to diffusion weighting from signal decay due to RF depolarization and $T_1$ relaxation. Number of repetitions of diffusion weighting gradients is given in Table 1. (B) Sequence diagram for CSSR acquisition of $^{129}$Xe dissolved in lung tissue. A/D, data sampling by analog–digital converter; CSSR, chemical shift saturation recovery; DP, dissolved phase; Exc, excitation pulse; $G_{(x,y,z)}$, gradient along {x,y,z}-axis; RBC, red blood cells; Sat, saturation pulse; TP, tissue/plasma.

TABLE 1 Parameters for diffusion-weighting part of sequence

| $G_0$ (mT/m) | 17.00/6.56 | 19.50/11.17 | 22.05/15.96 | 25.08 | 20.60 | 15.96 | 14.36 | 11.45 | 9.29 | 9.29 | 0 |
| $|G|$(mT/m) | 34.00/13.12 | 39.00/22.34 | 44.10/31.97 | 50.16 | 41.21 | 31.91 | 28.72 | 22.89 | 18.59 | 18.58 | 0 |
| $\Delta$(µs) | 540/1140 | 740/1140 | 920/1140 | 1140 | 1400 | 1660 | 1960 | 2280 | 2620 | 3000 – |
| $b_i$(s/cm$^2$) | 0.03/0.04 | 0.10/0.12 | 0.25/0.25 | 0.62 | 0.78 | 0.78 | 1.03 | 1.03 | 1.03 | 1.55 | 0 |
| $N$ | 7/5 | 6/5 | 5 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 2 |
| $b$(s/cm$^2$) | 0.21/0.21 | 0.62/0.62 | 1.26/1.26 | 3.10 | 3.10 | 3.10 | 3.10 | 3.10 | 3.10 | 3.10 | 0 |

The peak magnitude $|G|$ of the sinusoidal gradient is twice $G_0$ as described in the text. The diffusion-weighting $b_i$ of an individual pulse pair is given by $3\gamma^2 |G|^2 \Delta^3/\pi^2$, the total $b$ value by $Nbi$ with $N$ the number of repetitions. In the first patient, diffusion times as low as 540 µs were used while in the other patients the 1140 µs diffusion time was repeated while varying the $b$ value.
129Xe resonance in red blood cells and tissue/plasma, followed by a spoiling gradient in order to destroy the dissolved-phase magnetization. The buildup of dissolved-phase signal was then measured at a given delay time after saturation using a Gaussian-shaped RF excitation pulse with ~27° flip angle centered on the dissolved phase. Sampled delay times were 3, 4, 5, 6, 7.5, 10, and 12.5 ms, and the spectrum of each delay time was averaged 4 times, resulting in ~1.6 s measurement time.

### 3.2 | In vivo measurements

This study was approved by the local institutional review board, and written informed consent was obtained from all patients. Nine COPD patients were included in the study (see Table 2 for patient demographics).

CT imaging was performed on the same day, and data were used to obtain independent $S/V_g$ estimates. Images were acquired in inspiration using a GE LightSpeed VCT (GE Healthcare, Milwaukee, WI) CT system with slice thickness 0.625 mm, 120 kV tube voltage, 85 mA tube current, and 0.4 s exposure time, and were reconstructed using a soft-tissue reconstruction kernel.

MRI was performed at 1.5 tesla (T) (Avanto, Siemens Healthcare GmbH, Erlangen, Germany) using a custom-built birdcage transmit and 16-channel receive coil tuned to the 129Xe resonance (Rapid Biomedical, Rimpar, Germany). Isotopically enriched 129Xe gas (92% 129Xe, Nukem Isotopes Imaging GmbH, Alzenau, Germany) was hyperpolarized using a commercially available polarizer (9810, Polarean, Durham, NC) to about 25% polarization. Starting from residual volume, patients inhaled a gas mixture containing $V_{Xe} = 500$ to 600 mL 129Xe; $V_{N2} = 400$ to 500 mL N2; and a variable amount of air to achieve a total gas volume of one-third of the patient’s forced vital capacity, as determined by spirometry, and held their breath during data acquisition. Subsequently to the diffusion measurements, high-resolution ventilation images were obtained in the same breathhold. For this purpose, a TrueFISP sequence with stack-of-stars trajectory was used, TR/TE 3.73/1.80 ms, flip angle 10°, 85 projections, 16 slices, resolution 2.4 × 2.4 × 15 mm3. Total scan time for ADC/CSSR measurements and ventilation imaging was ~10 s. Ventilated volume $V_{Vent}$ was computed using a threshold-based method and, for comparison of results from ADC measurements with first-order fits, free diffusivity was estimated by Refs. [21-23]

$$D_{0,est} = \frac{V_{Vent}}{\frac{V_{Xe}}{0.059} + \frac{V_{N2} - V_{Xe}}{0.140}} \text{cm}^2 \text{s}^{-1}, \tag{5}$$

where we have neglected the effects of change of N2 fraction in air due to admixture of additional N2.

### 3.3 | Phantom measurements

A phantom measurement in a Tedlar bag (Jensen Inert Products, Coral Springs, FL) of size 3 L containing 600 mL hyperpolarized xenon, and 2400 mL nitrogen was performed. $S/V_g$ for this bag was estimated as 0.4 cm$^{-1}$ based on its geometrical dimensions. The scan was started several minutes after the phantom was placed in the magnet to avoid effects from bulk gas movement. Notice that we cannot expect our pulse sequence, in principle, to be able to accurately measure $S/V_g$ in this case because the waiting time used is not long enough to flatten out the edge enhancement. Because only a small fraction of spins senses the walls of the bag during our measurement window, we assume that we are measuring to good approximation free diffusion in this case and expect an approximately constant diffusivity as function of time.

### 3.4 | Data analysis

In order to disentangle the decay of hyperpolarized magnetization from the effects of diffusion weighting, the imaging data were normalized by the signal of the FID before application of the first diffusion-weighting gradient. This was done.
for each of the 16 receive channels individually. The magnitude of the signals in all voxels within the ventilated area of the lung was added together to obtain $S(\Delta)$ and then divided by the magnitude of the signal of the unweighted acquisition $S_0$. The whole-lung apparent diffusion coefficient at each diffusion time was then calculated by

$$D_{\text{app}}(\Delta) = \frac{1}{b} \ln \left( \frac{S(\Delta)}{S_0} \right),$$

where $b$ is the product of the $b$ value of an individual diffusion-weighting gradient pair with the number of repetitions. Whole-lung $S/V_g$ was then estimated in 2 ways:

- First-order fit: Assuming the series in Equation (3) is approximated well by the first 2 terms, a linear function was fit to the whole-lung data points of the fourth to seventh diffusion time measurement versus $\sqrt{\Delta}$ to obtain estimates of $S/V_g$, whereas the other measurements were discarded. $D_0$ was treated as variable parameter.
- Second-order fit: To account for possible influences of higher-order terms, a term proportional to $\Delta$ was included for fitting as proposed in Ref. [22] In order to stabilize the fit in the range of very short diffusion times, a fixed $D_0$ of 0.14 cm$^2$/s was assumed, and all measurements with constant $b$ value (4th-10th diffusion time) were used for fitting.

ADC and $S/V_g$ maps were also created for qualitative assessment by voxel-wise application of Equation (6) and subsequent fitting.

$S/V_g$ values were used to estimate average pore sizes $l_g = 6/(S/V_g)$, assuming a spherical geometry together with the estimates of diffusion length $l_D = \sqrt{D_0 \Delta}$ and dephasing length $l_G = \sqrt{D_0 / |\gamma G|^2}$. The shortest of these lengths determines the regime in which measurements are carried out, which are free/Gaussian diffusion ($l_D$), motional-narrowing regime ($l_S$) where pores are traversed many times during diffusion-weighting, and localization regime ($l_G$) where only a thin layer at edges contributes to the signal (see Figure 1B).

Phase correction of zeroth and first order was applied to the CSSR spectra, and the real part of the gas and dissolved phase was integrated to find the fraction $F$ of $^{129}$Xe in the dissolved phase as function of delay time $t_0$. The flip angle of the off-resonant gas excitation by the Gaussian excitation pulse of the dissolved phase was determined by an additional calibration spectrum, with direct excitation of the gas phase. The short-time Butler approximation for CSSR was used for determination of $S/V_g$,

$$F(t_D) \approx F_0 + \lambda \frac{S}{V_g} \sqrt{\frac{4D_{d}t_D}{\pi}},$$

where $F_0$ is an offset parameter to account for saturation inaccuracies; $\lambda \approx 0.1$ is the Ostwald coefficient of $^{129}$Xe in the lung tissue and was assumed to be the same for the whole dissolved phase for simplicity; and $D_d \approx 3.3 \times 10^{-6}$cm$^2$/s is the diffusivity of $^{129}$Xe in lung tissue.$^{9,25}$

In CT images, the lung was segmented semiautomatically (3D Slicer with Chest Imaging Platform extension, version 4.10.2). Further, voxels with CT values outside the range from $-1000$ HU to $-500$ HU were excluded, and the gas volume $V_g$ per tissue mass $m_t$ computed for each voxel as previously described in Ref. [26] The surface-area per voxel volume was estimated for each voxel using

$$\frac{S}{V_{\text{voxel}}} \approx e^{6.84 - 0.32 \frac{\text{HU}}{\text{cm}^{-1}}},$$

which was previously obtained by comparison with histology.$^{26-28}$ The lung surface area was determined by multiplying these values with the voxel volume and summing over the whole lung. Gas volume fraction was computed for each voxel by subtracting tissue volume fraction computed, as in Ref. [26] from 1. The total gas volume in the lung was then obtained by multiplication with the voxel volume and summation over all voxels in the mask. Finally, $S/V_g$ was computed as ratio of whole-lung surface area and whole-lung gas volume.

3.5 Statistical analysis

Correlations among $S/V_g$ measurements as well as with clinically established measures were assessed using Pearson’s correlation coefficient. Deviations of parameters from different methods were assessed using Bland-Altman analysis as well as Wilcoxon signed-rank tests. The significance level was set to 0.05 two-sided.

4 RESULTS

4.1 Imaging results

Figure 3 shows representative diffusion-weighted and corresponding nonweighted images in 1 of the patients, along with phase difference maps, ADC maps, $S/V_g$ maps, and CT images for comparison. It becomes apparent that substantial phase errors are introduced by the diffusion-weighting gradients, which are mostly consistent with expected phase accumulation from concomitant fields.$^{29}$

4.2 Time-dependent diffusion measurements

It was found in the first patient that at very low diffusion times, when $b$ values could not be chosen as high as at later
FIGURE 3  Representative imaging results from patient 6 with predominantly lower-lobe emphysema. (A) Inspiratory CT images at similar slice locations as in $^{129}$Xe MRI, emphysematous regions with CT density below –950 HU are shown as red overlay. (B) $^{129}$Xe images without diffusion weighting showing hypoventilation/ventilation defects predominantly in the lower lungs. (C) Images at lowest diffusion time, 1140 µs. (D) Phase difference of images in (B) and (C) corresponds well with predicted phase errors due to concomitant fields depicted in (E). (F) ADC map for shortest diffusion time of 1140 µs, $b$ value 3.10 s/cm$^2$. (G) ADC map for longest diffusion time of 3000 µs. It is apparent that the ADC map at higher diffusion time is more homogeneous which is attributed to eddy currents and the fast spiral readout. $S/V_s$ ratio maps for (H), ADC measurements with first-order fit, I, ADC measurements with second-order fit, J, computed tomography analysis showing $S/V_s$ maps according to Ref. [26]
diffusion times due to hardware and physiological constraints, the ADCs did not follow the expected behavior, as in Equation (3), but rather deviated to higher values. It was concluded that no reliable measurements were possible using these very small \( b \) values. The effects of varying the \( b \) value at fixed diffusion time were investigated in the other patients, and a qualitatively similar behavior was observed. A clear and approximately linear decline in the time-dependent diffusion coefficients versus square root of diffusion time was observed for diffusion times from 1140 µs with constant \( b \) value (see Figure 4). For the constant \( b \) value measurements in the phantom, ADCs were constant as function of diffusion time within 1.5% maximum deviation from the mean ADC of 0.1032 cm\(^2\)/s. Figure 5 shows representative results from short-time CSSR measurements.

### 4.3 \( S/V_g \) quantification

Results for \( S/V_g \) from all measurement methods and \( D_0 \) from gas diffusion measurements are summarized in Table 3. Group mean \( S/V_g \) and SD were 125.9 ± 43.3 cm\(^{-1}\) for CSSR, 75.0 ± 15.5 cm\(^{-1}\) (first-order fit) and 122.3 ± 32.8 cm\(^{-1}\) (second-order fit) for the gas diffusion measurements, and 159.5 ± 50.9 cm\(^{-1}\) for CT. The group mean value for free diffusion was 0.122 ± 0.012 cm\(^2\)/s, which tended to be higher than free diffusion as estimated using Equation (5), 0.113 ± 0.003 cm\(^2\)/s, \( P = .051 \). \( S/V_g \) estimated for the phantom from ADC measurements using a first-order fit was 17.1 ± 4.0 cm\(^{-1}\) and free diffusivity 0.111 ± 0.002 cm\(^2\)/s.

Scatter plots as well as Bland-Altman plots for comparison of \( S/V_g \) measurements are shown in Figure 6. There were strong correlations of \( S/V_g \) values from ADC and CSSR measurements with \( r = 0.840, P = .005 \) (first-order fit), and \( r = 0.923, P < .001 \) (second-order fit). \( S/V_g \) values derived from CSSR were significantly higher compared to gas diffusion measurements for first-order fits, \( P = .004 \), but not for second-order fits, \( P = .496 \). The average ratio of \( S/V_g \) ADC and \( S/V_g \) CSSR was 0.631 ± 0.139 (first-order fit) and 1.004 ± 0.157 (second-order fit). Bland-Altman analysis indicated a strong dependence of the difference of \( S/V_g \) values from both methods on mean \( S/V_g \), \( r = 0.914, P < .001 \), for first-order fits, whereas there was only a nonsignificant trend in the case of second-order fits, \( r = 0.587, P = .096 \).

Only a nonsignificant trend for a correlation between \( S/V_g \) from CT and ADC measurements with first-order fit was observed, \( r = 0.568, P = .110 \), whereas there was a significant correlation for \( S/V_g \) obtained by second-order fits, \( r = 0.729 \) and \( P = .026 \). \( S/V_g \) from ADC measurements was significantly smaller than CT in both cases, \( P = .004 \) (first-order fit) and \( P = .020 \) (second-order fit).
S/V₉ values from CSSR correlated significantly with those derived from CT, $r = 0.705, P = .034$, but were significantly smaller, $P = .020$.

No significant correlation between estimated and free diffusivities from first-order fits was found. Group mean effective pore sizes $l₉$ were $829.6 \pm 165.9$ µm for first-order fits and $530.9 \pm 185.3$ µm for second-order fits. Figure 1B shows the corresponding points within the phase plot of diffusion regimes according to Hürlimann et al.²⁴

### 4.4 Correlations with clinical measures

There was a significant correlation of S/V₉ as obtained from ADC measurements, with diffusing capacity for carbon monoxide as percent of predicted value for first-order fits, $r = 0.724, P = .028$, and a nonsignificant trend for a correlation for second-order fits, $r = 0.657, P = .055$ (Figure 7). This correlation was not significant in the case of S/V₉ derived from CSSR, $r = 0.450, P = .225$, and derived from CT, $r = 0.526, P = .146$. There was a significant correlation of S/V₉ from CT, with forced expiratory volume in 1 s as percent of predicted value, $r = 0.739, P = .023$.

### 5 DISCUSSION

We investigated the potential for determining S/V₉ ratios in vivo using $^{129}$Xe ADC measurements at short diffusion times under the assumption of the first-order approximation of the short-time series, Equation (3), and by additional inclusion of the next order term. In a second step, we compared the
Correlation and Bland–Altman analysis of S/\(V_g\) from ADC measurements with results from CSSR and CT imaging. (A) For first-order fits, results from ADC measurements and CSSR are strongly correlated, \(r = 0.840, P = .005\), but a linear fit through the points clearly deviates from the line of identity (dashed line). (B) There is also strong correlation for second-order fits, \(r = 0.923, P < .001\), a linear fit through the points lies close to the line of identity. (C) Bland–Altman analysis suggests a relationship of systematic deviations and mean S/\(V_g\) through significant correlation in the case of first-order fits, \(r = 0.914, P < .001\), only a nonsignificant trend is observed for second-order fits, \(r = 0.587, P = .096\). (D) Only a trend for a correlation between S/\(V_g\) from ADC first-order fits and CT is observed, \(r = 0.568, P = .110\). (E) Significant correlation in the case of second-order fits, \(r = 0.729, P = .026\), most points lie below the line of identity. (F) Systematic deviations between S/\(V_g\) from ADC measurements and CT also correlate with mean S/\(V_g\) for first-order fits, \(r = 0.876, P = .002\), but not for second-order fits, \(r = 0.552, P = .124\).
The results of Figure 3 indicate that in large objects such as human lungs it is not possible to neglect the phase errors due to concomitant fields and potentially also eddy currents at useful $b$ values such that an imaging readout is required. For the measurements with a nominal $b$ value of $3.10 \text{ s/cm}^2$, the diffusion-weighting caused by the imaging gradients with a $b$ value of $0.06 \text{ s/cm}^2$ at the outer regions of $k$ space seems negligible.

Apart from statistical errors, it does not seem to be entirely clear what is causing the deviation of ADCs at low diffusion times or low $b$ values, respectively, from the expected behavior. One explanation would be a nonmonoexponential signal decay, for example, of biexponential or kurtosis form. However, we think that because the change of diffusion times between sequence versions did not change the behavior essentially, the deviations are at least partly attributable to susceptibility effects, which cause additional background gradients close to the alveolar surfaces within lung tissue. These additional gradients disturb the intended diffusion weighting, and it has been found previously in experiments with $^3\text{He}$ in human lungs that this leads to an increase of ADCs with decreasing $b$ value. It thus seems necessary to acquire all ADCs using the same $b$ value, which needs to be high enough to avoid too strong of a susceptibility and other systematic effects and low enough to remain within the low $b$ value limit. It is conceivable that susceptibility effects also disturb our measurements by changing the ADC as a function of diffusion time. This appears to play only a minor role, however, because it was found from theoretical considerations that the ADC as obtained from bipolar gradient pulses without use of refocusing pulses always increases as a function of diffusion time in the presence of a spatial Larmor frequency distribution.

The phase plot of diffusion regimes in Figure 1B indicates that our measurements are carried out in the border region of still approximately free/Gaussian diffusion and localization regime such that Equation (6) should hold approximately for low diffusion-weighting $bD_0$, but that there are influences of the transition to the localization regime, which require the introduction of a waiting time into the pulse sequence. Carl et al investigated the influence of the waiting time on measured values, and our $2000 \mu\text{s}$ waiting time is close to the $\Delta$ to $2\Delta$ range suggested in Ref. [13] for the shortest diffusion times. The associated diffusion length of this waiting time is roughly the size of a healthy alveolus, and the corresponding equilibration time also lies in the range of the quantity $l_s\sqrt{\Delta/D_0}$ suggested in Ref. [13]. Further research is necessary to assess the influence of the waiting time on measured values.

The results from our phantom measurement indicate that the proposed pulse sequence can measure ADCs at the
The fact that the S/Vg values from 129Xe ADC measurements correlate more strongly with \(D_{LCO}\) whereas S/Vg from CT correlates more strongly with forced expiratory volume in 1 s, may suggest that the proposed method is more specifically probing the alveolar microstructure as opposed to larger structures relevant for breathing mechanics. Future work will show the relative sensitivity of short-time diffusion measurements for disease, which has been shown to be increased compared to longer diffusion times in certain diseases in proton MRI.39

A limitation of our study was the relatively low number of patients included. Both CSSR and ADC measurements have the limitation that results may be influenced to varying degree by large airways as opposed to the intended measurement in the lung parenchyma. Another limitation is the assumption of a single value for the free diffusivity for the whole lung, which could lead to errors in S/Vg quantification.18 In addition, the pulse sequence developed was only capable to measure ADCs reliably down to 1140 µs diffusion time, which is considerably longer than the ~500 µs previously described as necessary for accurate assessment of S/Vg in healthy human lungs using 129Xe ADCs and first-order fits.12,13 It was previously proposed to truncate the Mitra series after the second-order term to avoid systematic errors based on simulations of 129Xe diffusion in a geometry resembling healthy human lung.22 We found that this in practice makes an assumption on free diffusion necessary in order to stabilize the fit in the range of very short diffusion times. A limitation of our comparison with S/Vg from CT is the inhomogeneity in 129Xe MR signal throughout the lung, which could introduce a bias because emphysematous regions tend to be less ventilated. The normalization of imaging data by FID signals does not account for inhomogeneity in the decay of hyperpolarized magnetization at voxel level, thereby potentially introducing a small bias in the ADC maps.

In practice, at a given TE, the achievable b values for low diffusion times are mainly restricted by the physiological limits for peripheral nerve stimulation and not so much by gradient slew rate or maximum amplitude. Apart from increasing the TE, for example, by going to lower field,40 possible ways around this problem would be novel hardware developments with matrix gradient coils.41,42 Stronger gradients would push the acquisition further into the localization regime, however, potentially invalidating the assumptions on approximately free diffusion. Alternatively, one could make use of refocusing pulses to create spin echoes and thus prolong the useful range of TEs. This would also have the advantage that, by virtue of gradient waveform symmetrization around the refocusing pulses, the phase errors due to concomitant fields could be canceled,43 potentially enabling use of the FID-based approach proposed in Ref. [13] We have found, however, that this solution is not very beneficial in practical implementations, mainly because a large number of refocusing pulses

\[ b = \text{value of 3.10 s/cm}^2 \text{ with good accuracy. The observed deviations of } 1.5\% \text{ from the mean value are within typical error levels due to gradient infidelity}.32 \text{ Future work should focus on increasing accuracy by characterizing such effects.}

Using the data points with constant b value, we found a clear decrease of whole-lung ADC with increasing diffusion time in all patients, as must be the case in any medium with boundaries. The values for the free diffusivity \(D_0\) from the first-order fits are on average somewhat higher than the values estimated using Equation (5) but still lower than the literature value of 0.14 cm²/s for the diffusion of 129Xe atoms dilute in air.33 Unrestricted second-order fits would give a group mean free diffusion of 0.147 ± 0.015 cm²/s and 0.127 cm²/s in the phantom. Possible explanations for the deviation of free diffusivity in patients are susceptibility effects or the influence of higher order terms in Equation (3). It also seems possible that the values obtained from Equation (5) are only a relatively rough estimate and may thus not be suitable for determining \(D_0\) for the fit.

The S/Vg values lie in a roughly realistic range both for CSSR and gas-phase diffusion measurements when compared to results of histological studies and estimates from diffusion measurements.15,26,34,35 Whereas S/Vg from first-order fits appeared to be somewhat underestimated compared to CSSR and CT, there was a very good agreement between S/Vg from second-order fits and CSSR assuming a free diffusion of 0.14 cm²/s. These values are also in fair agreement with those from quantitative CT imaging, which was validated by histology in humans before.26 Future work should concentrate on direct validation of S/Vg values using results from histology, as has also been done for CSSR in a mouse model of emphysema.36 It should be noted that, also in microscopy, the apparent surface area is a function of experimental parameters such as microscopic resolution.37 The answer to the question what the true S/Vg of the lung thus depends on definition and is to some degree arbitrary. Microscopy also does not account for the alveolar surface lining layer, which is believed to reduce the alveolar surface by some 25% to 50% compared to the epithelial surface.37

In theory, it should be possible to use the combination of time-dependent gas diffusion and CSSR measurements to obtain estimates of the product of Ostwald coefficient and square root diffusivity of 129Xe within the lung parenchyma36 by using results from ADC measurements as ground truth in Equation (7). Xie et al found evidence that the ratio of S/Vg values estimated by ADC and CSSR measurements correlates with disease severity as measured by spirometry.15 It does not seem clear, however, whether we are really capturing alterations of tissue composition rather than the influence of higher-order terms in Equation (3) or possibly still other effects. We think, however, that the simultaneous acquisition of short-time diffusion measurements offers additional and potentially clinically relevant information on lung tissue microstructure.

\[ D = \text{value of } 3.10 \text{ s/cm}^2 \text{ with good accuracy. The observed deviations of } 1.5\% \text{ from the mean value are within typical error levels due to gradient infidelity}.32 \text{ Future work should focus on increasing accuracy by characterizing such effects.}

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has to be applied to prolong the apparent T₂ sufficiently and because the refocusing pulses destroy the hyperpolarized magnetization rapidly and also require additional crusher gradients to destroy spurious FID signals, which in turn interferes with the intended diffusion weighting. It would be possible to reduce the free diffusivity by using a different gas mixture or different tracer gas, thus relaxing the requirements on the sequence parameters. On the other hand, working at the border of the short-time regime could also be advantageous in that higher-order terms of the expansion in Equation (3) could be captured by including them in the fit and S/Vg still be quantified accurately provided free diffusion is known to sufficient accuracy. Finally, Laun et al recently found that by nulling the first gradient moment of the diffusion-weighting gradients, the second-order term is effectively removed from the series in Equation (3). The same holds true in oscillating-gradient sequences, thus potentially enabling more accurate S/Vg measurements.

6 | CONCLUSION

Quantification of the lung surface-to-volume ratio by ¹²⁹Xe ADC measurements at short-time scales is feasible in COPD patients and provides clinically relevant information without the need for ionizing radiation or invasive tissue sampling.

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