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Reproducibility of pulmonary magnetic resonance angiography in adults with muco-obstructive pulmonary disease

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Abstract

Background: Recent studies support magnetic resonance angiography (MRA) as a diagnostic tool for pulmonary arterial disease.

Purpose: To determine MRA image quality and reproducibility, and the dependence of MRA image quality and reproducibility on disease severity in patients with chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF).

Material and Methods: Twenty patients with COPD (mean age 66.5 ± 8.9 years; FEV1% = 42.0 ± 13.3%) and 15 with CF (mean age 29.3 ± 9.3 years; FEV1% = 66.6 ± 15.8%) underwent morpho-functional chest magnetic resonance imaging (MRI) including time-resolved MRA twice one month apart (MRI1, MRI2), and COPD patients underwent non-contrast computed tomography (CT). Image quality was assessed visually using standardized subjective 5-point scales. Contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR) were measured by regions of interest. Disease severity was determined by spirometry, a well-evaluated chest MRI score, and by computational CT emphysema index (EI) for COPD.

Results: Subjective image quality was diagnostic for all MRA at MRI1 and MRI2 (mean score = 4.7 ± 0.6). CNR and SNR were 4 43.8 ± 8.7 and 50.5 ± 8.7, respectively. Neither image quality score nor CNR or SNR correlated with FEV1% or chest MRI score for COPD and CF (r = 0.239–0.248). CNR and SNR did not change from MRI1 to MRI2 ($P = 0.434$–0.995). Further, insignificant differences in CNR and SNR between MRA at MRI1 and MRI2 did not correlate with FEV1% nor chest MRI score in COPD and CF (r = −0.238–0.183), nor with EI in COPD (r = 0.100–0.111).

Conclusion: MRA achieved diagnostic quality in COPD and CF patients and was highly reproducible irrespective of disease severity. This supports MRA as a robust alternative to CT in patients with underlying muco-obstructive lung disease.

Keywords

Magnetic resonance angiography, functional imaging, cystic fibrosis, chronic obstructive pulmonary disease

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Introduction

Many chronic pulmonary and systemic diseases lead to the development of pulmonary hypertension (1,2). In the diagnostic work-up of pulmonary arterial diseases, cross-sectional imaging plays an important role in the diagnosis of causative pulmonary conditions and to assess pulmonary arterial morphology. Thus, computed tomography angiography (CTA) developed into the primary diagnostic tool to assess the pulmonary vasculature such as in acute pulmonary embolism (PE), and as part of diagnostic work-up for pulmonary hypertension (3,4). However, the radiation exposure associated with CTA is known to be a risk factor for the development of breast cancer and other malignancies and should therefore be avoided especially in certain patient groups such as young radiation-sensitive patients (5,6). In addition, in patients with renal insufficiency or with severe allergic predisposition, the use of iodinated contrast material may be contraindicated (7). Magnetic resonance imaging (MRI) with angiography (MRA) were developed into a radiation-free alternative for diagnosing acute PE, and further work also indicate a role for chronic-thromboembolic pulmonary hypertension and other cardio-pulmonary vascular anomalies (8–11). Previous studies showed that technically adequate MRA of the pulmonary arteries can detect, in particular, central and segmental PEs with high negative predictive value, sensitivity, and specificity (12–14). Even though MRA shows good diagnostic accuracy at specialized centers, concerns regarding robustness and diagnostic image quality especially in patients with limited ability to cooperate and breath-hold during relatively long acquisition times are limiting a more widespread use (7). Though these data indicate that in patients with acute and symptomatic PE MRA can achieve good diagnostic results, it is not clear whether underlying chronic lung diseases, such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF), may influence diagnostic quality of pulmonary MRA. It may be that lung disease per se may affect image quality, especially hyperinflation and tissue loss with mosaicism, and emphysema, apart from patient cooperativity and dyspnea leading to breathing artifacts similar to otherwise healthy patients with acute PE (10,15). In muco-obstructive lung disease, MRA may be part of routine protocols, or performed specifically to assess PE or other pulmonary arterial conditions in addition to underlying lung disease (16,17).

The aim of the present study was to determine the image quality of MRA, its reproducibility, and their dependence on disease severity in 20 patients with COPD and 15 patients with CF in a stable clinical condition by two chest MRI examinations one month apart.

Material and Methods

Study population

This retrospective study was approved by the institutional ethics committee (reference no. S-646/2016). It should be noted that patient data were first described elsewhere, but present analyses were not part of the original study (18). Full body plethysmography (MasterScreen Body, E. Jaeger, Hoechberg, Germany) was performed on the day of MRI acquisition according to guidelines of the European Respiratory Society and the standards of the American Thoracic Society (ATS) (19,20). The diagnosis of COPD was made according to established criteria by GOLD consortium (21). The diagnosis of CF was based on clinical symptoms confirmed by increased sweat Cl^- concentrations ($\geq$60 mmol/L) and CF transmembrane conductor mutation analysis. All patients must not be hypersensitive to gadolinium-based contrast agents and must have a glomerular filtration rate $\geq$30 mL/min. Patients with COPD had to be aged $\geq$40 years, with post-dilatator forced expiratory volume in 1 s in percent predicted (FEV1%) $\geq$30% and FEV1/FVC <70%. Patients with CF had to be aged $\geq$18 years with a pre-bronchodilator FEV1% predicted at baseline to be $\geq$30%. Both MRI scans were performed in a stable clinical condition, as previously described (22,23). In total, 35 patients (20 with COPD and 15 with CF) completed both MRI examinations, and FEV1% and chest MRI score did not change between the MRI examinations as published previously (Table 1, Supplemental Figure S1) (18).

MRI and CT

Image acquisition. Standardized MRI including MRA was performed at baseline (MRI1) and one month later (30.0 $\pm$ 2.5 days; MRI2) using an identical 1.5-T scanner and protocol (Magnetom Aera, Siemens Healthineers, Erlangen, Germany) as published previously (18,24). For MRA, a high-spatially resolved spoiled 3D gradient echo sequence with parallel imaging (FLASH; Siemens Healthineers, Erlangen, Germany) was performed before and in two phases after contrast material injection (0.05 mmol/kg body weight of gadobutrol [Gadovist; Bayer Schering AG,

Table 1. Patient demographics.

	COPD	CF	Both
No. of patients	20	15	35
Age (years)	66.5 $\pm$ 8.9	29.3 $\pm$ 9.3	50.6 $\pm$ 20.7
Sex (M / F)	15 / 5	13 / 2	28 / 7
History of smoking	20	2	22
Pack years	52.3 $\pm$ 22.2	0.7 $\pm$ 0.2	47.6 $\pm$ 26.8
BMI (kg/m^2)	25.1 $\pm$ 3.7	21.8 $\pm$ 2.8	23.7 $\pm$ 3.7
FEV1%	39.2 $\pm$ 8.8	66.6 $\pm$ 15.3	50.9 $\pm$ 18.1
Chest MRI score	14.3 $\pm$ 3.5	25.9 $\pm$ 6.4	19.3 $\pm$ 7.6
EI (%)	23.6 $\pm$ 11.0	—	—

Values are given as mean $\pm$ SD.
BMI, body mass index; CF, cystic fibrosis; CNR, contrast-to-noise ratio; COPD, chronic obstructive pulmonary disease; EI, emphysema index; FEV1%, forced expiratory volume in 1 s percent predicted; MRI, magnetic resonance imaging.

Germany]; rate of 3–5 mL/s with power injector, followed by 30 mL saline chaser). The first phase was timed so that the middle of the contrast bolus arriving in the pulmonary trunk should meet the center of the k-space acquisition. Individual circulation time was determined by a time-resolved MRI perfusion study as previously described at identical injection rate and contrast dosing, so that maximum contrast dose (0.1 mmol/kg body weight) was split for perfusion study and angiography (18). Mean acquisition time of one MRA phase was 16.0 ± 0.7 s, with a fixed delay of 10 s in between phases for short respiration. The phase with the best subjective enhancement of pulmonary arteries was used for further analysis (MRI1: 31 times first and four times second phase, MRI2: 29 times first and six times second phase). For further protocol details, see electronic supplementary material.

In patients with COPD, clinically indicated non-contrast enhanced CT (SOMATOM Definition AS; Siemens Healthineers, Erlangen, Germany) was performed within 2 ± 3 days of baseline MRI (collimation = 0.6 mm, pitch = 1.5, tube potential = 120 kVp, and tube current = 70 mA [total effective dose = 4.6 ± 1.8 mSv]) and iteratively reconstructed with i40f\3 and i70f\3 kernels and a slice thickness of 1.0 mm with an increment of 0.7 mm.

Image assessment. All examinations were assessed by two readers with >2 and >12 years of experience in chest MRI using standardized questionnaires (Supplemental Figures S2 and S3). MRI and CT were assessed for image quality and vessel sharpness. MRI was additionally assessed for contrast timing and enhancement of pulmonary arteries. Moreover, the presence of artifacts (general motion artifact, respiratory artifact, pulsation artifact, ringing artifact, and other artifacts) was evaluated using a 5-point Likert scale (1 = non-diagnostic, 2 = poor/many artifacts, 3 = sufficient/some artifacts, 4 = good/few artifacts, 5 = excellent/no artifacts). The maximum number of visible pulmonary arterial branching points and the minimal distance between most peripheral visible vessel and pleura were determined for segments 1, 4, and 10 in both lungs. A region of interest (ROI) analysis was performed to determine signal intensity in the pulmonary trunk, main pulmonary artery, lobar artery, and segment-1, segment-4, and segment-10 artery each, in order to compute contrast-to-noise ratio (CNR), signal-to-noise ratio (SNR), and vessel-to-background ratio (VBR) as described previously (25–27). In addition, MRI studies were assessed for lung disease severity by a single reader (MOW) using the well-evaluated chest MRI score for muco-obstructive lung disease (18,24,28). CT scans (reconstruction kernel i40f\3) were subjected to well-evaluated in-house software YACTA (version v2.9.1.22) to compute the emphysema index (EI) as previously described (29,30).

Statistical analyses

Data were analyzed using Prism version 9.1.0 (GraphPad Software, LLC) employing the paired *t*-test and Wilcoxon signed rank test as appropriate to compare MRI1 and MRI2, and the Pearson correlation coefficient for correlations of image quality parameters with FEV1%, chest MRI score, and EI. Inter- and intra-rater agreement were assessed by Cohen's weighted kappa coefficient and Bland–Altman plots. Data are presented as mean ± standard deviation. A P value <0.05 was considered statistically significant.

Results

Diagnostic MRA image quality in patients with COPD and CF

Readers 1 and 2 disagreed to a low extent regarding the distance from the most peripheral vessel to the pleural surface ($P < 0.001$). Otherwise, inter- and intra-rater agreement for all other visually assessed parameters was "moderate" to "almost perfect" ($\kappa = 0.671$–0.932) (Supplemental Table S1, Supplemental Figure S4). In patients with COPD, subjective image quality was diagnostic in all MRA at MRI1 and MRI2, and all visually assessed qualitative parameters were rated as "good" with 4.2 ± 1.1 or higher (Table 2, Figs. 1 and 2). For example, the contrast enhancement of evaluated arteries was rated as "good" with 4.5 ± 0.6 at MRI1 and 4.4 ± 0.9 at MRI2 (Table 2, Fig. 1). CNR and SNR were 46.0 ± 9.3 and 52.7 ± 9.2, respectively (Fig. 3). In patients with COPD, sharpness of peripheral vessels and maximum number of branching points were rated higher, and minimal distance between most peripheral vessel and pleura was lower for CT than for MRI (Table 2).

Similarly, in patients with CF the subjective image quality was diagnostic for all MRA at MRI1 and MRI2, and visually assessed qualitative parameters were rated at least as "good" with 4.3 ± 0.8 or higher (Table 2, Figs. 1 and 2), while contrast enhancement was scored with a minimum average of 4.5 ± 0.8 for central and peripheral arteries (Table 2, Fig. 1). CNR and SNR were 40.8 ± 6.7 and 47.6 ± 6.8, respectively (Fig. 3).

MRA image quality is not associated with disease severity in COPD and CF

Regarding visually assessed quality parameters and quantitative parameters, we did not find differences between COPD and CF ($P = 0.220$–0.999).

In all MRA examinations of patients with COPD, none of the visually or quantitatively assessed parameters showed a significant correlation with FEV1% ($P = 0.133$–0.999), chest MRI score ($P = 0.156$–0.999) nor EI ($P = 0.201$–0.999) (Table 3, Supplemental Table S2).

Similarly, in patients with CF, no correlations of visual and quantitative image quality parameters with FEV1%

($P = 0.211$–0.999) nor chest MRI score were found ($P = 0.253$–0.999) (Table 3, Supplemental Table S2). This holds true when all patients are pooled ($P = 0.118$–0.999) (Table 3, Supplemental Table S2).

MRA is highly reproducible in COPD and CF

In patients with COPD, only the minimal distance between most peripheral vessel and pleura differed between MRI1 and MRI2 (mean difference = 1.8 ± 5.5; $P = 0.041$) (Table 2).

In patients with CF, only respiratory artifacts changed slightly between MRI1 and MRI2 (mean difference = 0.4 ± 0.6; $P = 0.028$) (Table 2).

For both groups taken together, only the maximal number of branching points (mean difference = 0.2 ± 1.0: $P = 0.011$) and minimal distance between most peripheral vessel and pleura (mean difference = 1.4 ± 5.9; $P = 0.049$) varied between MRA at MRI1 and MRI2 (Table 1, Fig. 3). All other parameters, especially CNR and SNR, did not change ($P = 0.091$–0.999) (Table 2, Fig. 3).

Reproducibility of MRA is not impaired by disease severity in COPD and CF

In patients with COPD, none of the mostly insignificant differences between MRA at MRI1 and MRI2 in the visually assessed parameters showed a correlation with either FEV1% or chest MRI score or EI ($P = 0.056$–0.999). In addition, the insignificant differences in SNR and CNR did not correlate systematically with either FEV1% or chest MRI score or EI ($P = 0.797$–0.955) (Table 4, Supplemental Table S3).

Similarly, in patients with CF, differences between MRA at MRI1 and MRI2 did not correlate with either FEV1% or chest MRI score ($P = 0.157$–0.999) (Table 4, Supplemental Table S3). Similar results were obtained for a pooled analysis of patients with COPD and CF.

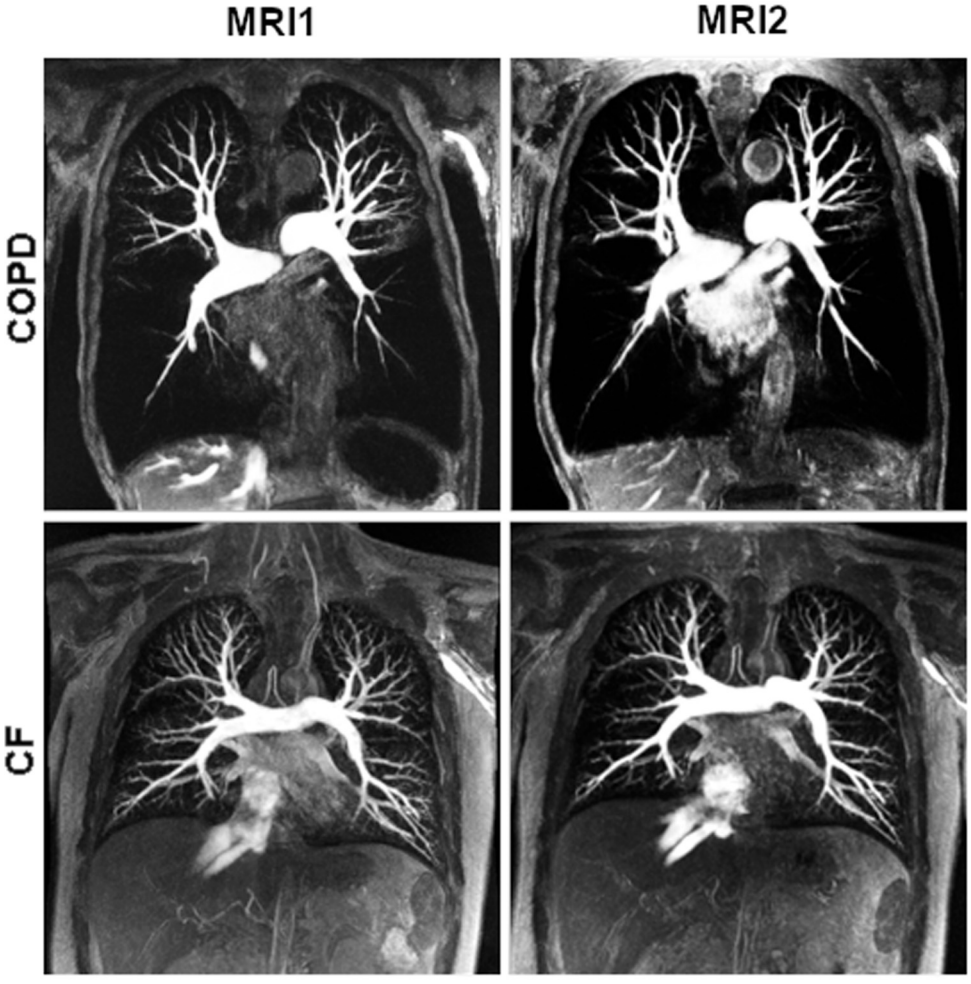

Fig. 1. Representative examples of pulmonary magnetic resonance angiography in patients with COPD and CF. MRI1 and MRI2 were acquired one month apart. Please note that images are shown as 20 mm maximum intensity projection for better visualization. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; MRI, magnetic resonance imaging.

Table 2. Image quality in patients with COPD and CF at two MRA examinations acquired one month apart.

	COPD			CF		Both	
	MRI1	CT	MRI2	MRI1	MRI2	MRI	MRI2
Image quality	4.8 ± 0.5	4.9 ± 0.4*	4.7 ± 0.6	4.6 ± 0.6	4.8 ± 0.5	4.7 ± 0.6	4.7 ± 0.6
Timing	4.6 ± 0.7		4.6 ± 0.8	4.8 ± 0.5	4.5 ± 0.8	4.7 ± 0.6	4.5 ± 0.7
Contrast enhancement							
Central arteries	4.6 ± 0.6		4.5 ± 0.8	4.8 ± 0.5	4.5 ± 0.6	4.7 ± 0.6	4.5 ± 0.7
Peripheral arteries	4.5 ± 0.7		4.3 ± 1.0	4.7 ± 0.8	4.5 ± 0.6	4.6 ± 0.7	4.4 ± 0.8
Central and peripheral arteries	4.5 ± 0.6		4.4 ± 0.9	4.8 ± 0.7	4.5 ± 0.6	4.6 ± 0.7	4.4 ± 0.8
Sharpness							
Central arteries	4.8 ± 0.5	5.0 ± 0.0†	4.5 ± 0.7	4.9 ± 0.3	4.7 ± 0.4	4.8 ± 0.5	4.6 ± 0.6
Peripheral arteries	4.4 ± 0.9	4.8 ± 0.4†	4.2 ± 1.1	4.3 ± 0.7	4.5 ± 0.5	4.3 ± 0.8	4.3 ± 0.9
Central and peripheral arteries	4.6 ± 0.7	4.8 ± 0.4‡	4.4 ± 0.9	4.6 ± 0.6	4.6 ± 0.5	4.6 ± 0.7	4.5 ± 0.8
Artifacts							
General motion	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0
Respiratory	4.7 ± 0.6	4.9 ± 0.3*	4.6 ± 0.7	4.3 ± 0.8	4.7 ± 0.4§	4.5 ± 0.7	4.6 ± 0.6
Pulsation	4.7 ± 0.6	5.0 ± 0.2*	4.7 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	4.6 ± 0.6	4.6 ± 0.5
Ringing	5.0 ± 0.0		5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0
Other	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0
Maximal number of branching points	3.4 ± 1.3	5.5 ± 1.7‡	3.3 ± 1.4	3.2 ± 1.7	2.9 ± 1.6	3.3 ± 1.5	3.1 ± 1.5§
Minimal distance vessel to pleura (mm)	10.8 ± 10.0	4.0 ± 1.3‡	12.6 ± 12.5§	13.5 ± 13.7	14.2 ± 14.1	11.9 ± 11.8	13.3 ± 13.2§

Values are given as mean ± SD of assessment on 5-point Likert scale.
*$P < 0.05$ MRI1 vs. CT.
†$P < 0.01$ MRI1 vs. CT.
‡$P < 0.001$ MRI1 vs. CT.
§$P < 0.05$ MRI1 vs. MRI2.
CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CT, computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

Table 3. Correlation of MRA quality parameters in patients with COPD and CF with lung disease severity.

	COPD			CF		Both	
	FEV1%	MRI score	EI	FEV1%	MRI score	FEV1%	MRI score
CNR	−0.060	−0.176	0.038	0.228	0.121	−0.166	−0.228
SNR	−0.063	−0.187	0.045	0.248	0.100	−0.160	−0.239
VBR	0.024	−0.211	−0.036	0.205	0.080	0.019	−0.092
Image quality	0.348	−0.156	−0.300	0.450	−0.145	0.173	−0.093
Timing	0.250	−0.159	−0.105	0.179	−0.207	0.221	0.116
Sharpness	0.248	−0.157	−0.136	0.074	−0.069	0.182	0.018
Respiratory artifacts	0.340	0.019	−0.153	0.129	0.009	0.071	−0.060

Values are given as Pearson correlation coefficients r.
CF, cystic fibrosis; CNR, contrast-to-noise ratio; COPD, chronic obstructive pulmonary disease; EI, emphysema index; FEV1%, forced expiratory volume in 1 s percent predicted; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SNR, signal-to-noise ratio; VBR, vessel-to-background ratio.

Discussion

The present study demonstrates that pulmonary MRA achieves diagnostic image quality and is highly reproducible in a patient cohort with moderate to severe muco-obstructive lung disease, namely COPD and CF. Our study shows that visually and quantitively assessed image quality was diagnostic in two MRA studies one month apart from all patients. Moreover, we show that neither MRA image quality nor MRA reproducibility

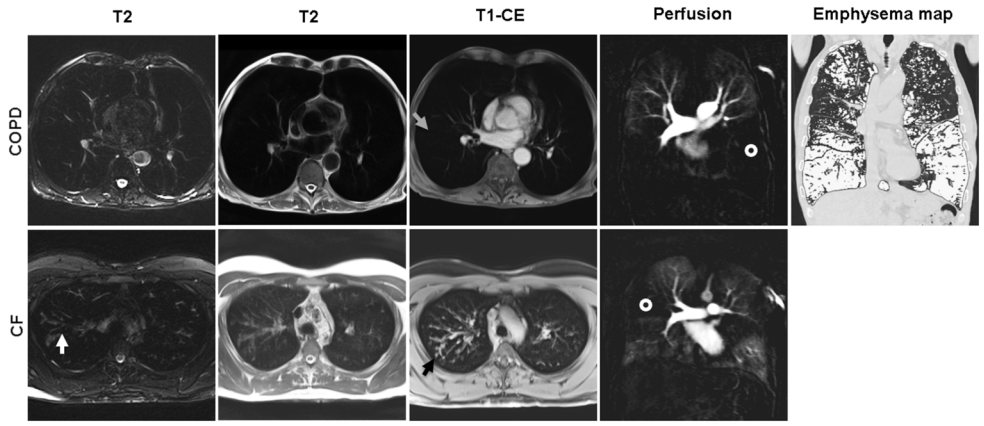

Fig. 2. Representative examples of morpho-functional magnetic resonance imaging in patients with COPD and CF (same patients as in Fig. 1) showing typical changes underlying the respective disease, such as bronchiectasis (white arrow), mucus plugging (black arrow), emphysema (gray arrow), and perfusion defects (white circles). For COPD, the emphysema map generated by YACTA software based on non-enhanced CT is also shown. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease.

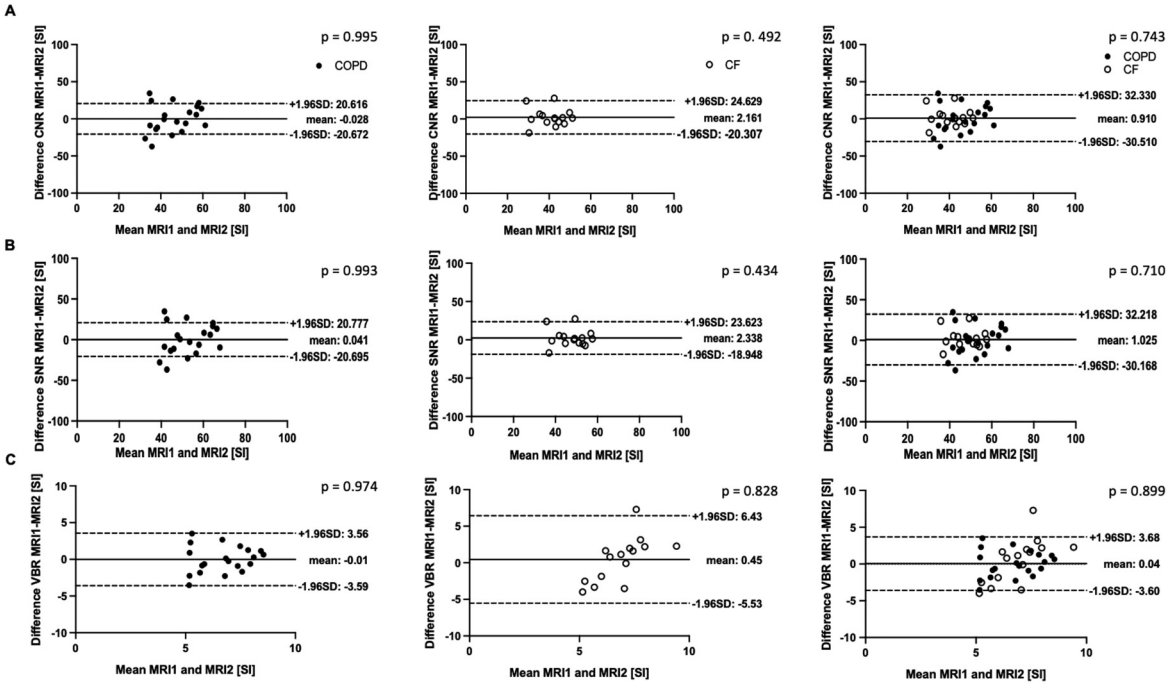

Fig. 3. Reproducibility of pulmonary magnetic resonance angiography in patients with COPD and CF. Bland–Altman plots for (a) CNR, (b) SNR, and (c) VBR comparing MRI1 and MRI2 in patients with COPD (black circles) and CF (white circles). Mean difference, limits-of-agreement, and *P* values are given for each panel. CF, cystic fibrosis; CNR, contrast-to-noise ratio; COPD, chronic obstructive pulmonary disease; SNR, signal-to-noise ratio; VBR, vessel-to-background ratio.

within one month is impaired by disease severity in either COPD or in CF.

In the PIOPED-III trial, poor arterial opacity and general motion artifacts were mostly responsible for technically inadequate MRA, while the rate of technically inadequate MRA varied substantially between participating centers (range = 11%–52%) (31,32). A reason for the low rate of diagnostic MRA in the multicenter PIOPED-III study could be variations in technical factors such as scanner, scan protocol, and amount of contrast agent between the centers, since it is known that these influence the quality of MRA (11,12,31–33). Since PIOPED-III was carried out from 2006 to 2008, MRA technique has evolved substantially (such as field-of-view excitation, variable readout gradients, parallel imaging) contributing to improvements in diagnostic quality (11,34). In our study,

Table 4. Correlation of reproducibility of MRA quality parameters in patients with COPD and CF with lung disease severity.

	COPD			CF		Both	
	FEV1%	MRI score	EI	FEV1%	MRI score	FEV1%	MRI score
Δ CNR	−0.237	0.008	0.111	0.153	−0.132	0.002	0.078
Δ SNR	−0.238	0.013	0.100	0.183	−0.174	0.008	0.080
Δ VBR	−0.036	0.116	0.127	−0.031	−0.081	−0.051	−0.062
Δ Image quality	−0.245	0.203	−0.186	−0.285	0.197	−0.191	0.106
Δ Timing	−0.212	0.136	0.018	−0.186	−0.268	−0.179	−0.132
Δ Sharpness	−0.133	−0.181	0.099	−0.309	−0.199	−0.284	−0.094
Δ Respiratory artifacts	−0.070	0.198	0.211	−0.160	−0.250	−0.018	0.041

Values are given as Pearson correlation coefficients r.
CF, cystic fibrosis; CNR, contrast-to-noise ratio; COPD, chronic obstructive pulmonary disease; EI, emphysema index; FEV1%, forced expiratory volume in 1 s percent predicted; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SNR, signal-to-noise ratio; VBR, vessel-to-background ratio.

contrast enhancement of pulmonary arteries and bolus timing were "good" (Table 2). Moreover, artifacts were rarely present. This is in line with other monocentric studies carried out more recently, which achieved diagnostic quality of MRA in up to 97.4% (7,12). In our study, the "good" image quality was mainly characterized by good vessel contrast (measured by CNR, SNR, contrast timing, and enhancement), vessel sharpness, and absence of artifacts. In particular, CNR and SNR were high overall in our study (Fig. 3). In comparison, previous studies of CTA using usual recording parameters (100–120 kV, iterative reconstruction, standard dose of contrast media) showed lower CNR and SNR in the range of 5–38 (35,36). It is interesting that these parameters also remained diagnostic in patients with COPD, although most of them suffered from pronounced emphysema.

Despite the overall "good" quality of MRA, some parameters relating to peripheral subsegment arteries, such as maximum number of branching points, were higher in non-enhanced CT compared to MRA (Table 2). This confirms the well-known lower resolution of pulmonary MRA than CT in general, so that subsegmental pulmonary emboli are more often overlooked using MRA than CTA (31). It should be noted that these are only recognized in 1% of cases on CTA (31). In addition, it is unclear to what extent embolisms in subsegment arteries are clinically relevant at all (12,37,38).

To determine the association of image quality with disease severity, we correlated visual and quantitative parameters with FEV1%, chest MRI score, and, for patients with COPD, the EI based on quantitative CT. Disease severity determined by FEV1% as well as chest MRI score were lower in COPD than in CF (Table 1) (18). However, we did not find a correlation of FEV1%, chest MRI score, or EI with SNR and CNR (Table 3, Supplemental Table S2). It should be noted that the thesis of Sostman et al. states that technical factors influence the quality of MRA more than personal factors, supporting the notion that disease severity did not significantly correlate with MRA quality in our study (32).

Most evaluated parameters did not differ between both MRI examinations within the same patient. Therefore, a high level of reproducibility can be assumed. In patients with COPD, only the minimum distance between vessel and pleura varied, while in patients with CF, the presence of respiratory artifacts differed. In both groups taken together, the maximum number of branching points and minimum distance between vessel and pleura changed between the MRI scans (Table 2). A possible reason for the differences in maximum number of branching points and minimum distance between vessel and pleura between the MRA, and thus an important limitation, may be the limited field of view in the ventro-dorsal direction so that segment-10 arteries were not completely depicted in some examinations. This resulted in a reduced number of branching points and an increased distance between vessel and pleura in the affected examinations. To optimize the scan volume, which is significantly influenced by patient positioning and the size of selected field of view, these factors should be optimized (39). The difference in the respiratory artifacts in patients with CF between examinations could be due to situational factors such as inexperience with breathing instructions. This thesis is strengthened by the fact that, similarly to image quality, our study showed, that the reproducibility of MRA quality is not influenced by disease severity. Further, reproducibility did not differ between patients with COPD and CF despite differences in disease severity (Tables 1 and 4, Supplemental Table S3). This suggests that repeated MRA within a patient with chronic muco-obstructive lung disease can be performed with similar diagnostic quality and may thus also be used for longitudinal monitoring of pulmonary arterial disease or follow-up of PE. As previous studies have shown, repeated intravenous administration of gadolinium-based contrast material can lead to deposits, particularly in the brain (40). However,

information from well-designed clinical studies supporting a link between deposition of gadolinium and the development of clinical sequelae in patients with normal renal function are still lacking (41). Further, we used a contrast agent with macrocyclic structure, of which it is thought that it yields less risk of dissociation and subsequent deposition in human tissues (42).

Our study was conducted with clinically stable patients with COPD and CF without pulmonary arterial disease such as PE, so that we were not able to assess diagnostic accuracy for the presence of pulmonary arterial disease. However, since the intention of this work was to determine the quality and reproducibility of MRA and not to make a comparison between MRA and CTA for diagnosing pulmonary embolism, as has already been done in several previous studies, this should not reduce the informative value of this study (13,43). It should be noted that all patients included in the present study showed impaired pulmonary perfusion as determined by 4D perfusion MRI in combination with the chest MRI perfusion score, which was stable between the two MRI timepoints as reported in our previous study (18). These perfusion abnormalities found in COPD and CF are generally comparable to perfusion abnormalities found in patients with acute or chronic PE (11,18,24). Since the number of participants in our study was limited, a validation of our study's results in larger cohorts of patients with chronic lung diseases should be performed.

In conclusion, the present study shows that in patients with chronic muco-obstructive lung diseases, leading to reduced pulmonary perfusion and vascularity such as COPD and CF, MRA can reliably achieve diagnostic image quality. Image quality was not affected by individual disease severity as determined by spirometry, chest MRI score, and EI. In other words, a non-diagnostic exam, artifacts, and reduced CNR and SNR could not be predicted by disease severity. Taken together, these results emphasize the potential role of pulmonary MRA as a sensitive non-invasive, radiation-free, and robust method for studying pulmonary arterial disease, particularly in centers that routinely perform MRA.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: HUK declares relationships with the following companies: Siemens, Philips, Bayer, Boehringer Ingelheim, Astra Zeneca, Merck Sharp Dohme. MOW, CPH, and ME declare advisory board membership with Boehringer Ingelheim unrelated to the present study. MOW declares study support by Vertex Pharmaceuticals.

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Supplemental material

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