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European Journal of Radiology 63 (2007) 76–83

EJR
EUROPEAN JOURNAL OF RADIOLOGY

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Assessment of the relationship between lung parenchymal destruction and impaired pulmonary perfusion on a lobar level in patients with emphysema

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Received 12 September 2006; received in revised form 15 January 2007; accepted 18 January 2007

Abstract

Purpose: To assess the relationship between lung parenchymal destruction and impaired pulmonary perfusion on a lobar level using CT and MRI in patients with emphysema.
Material and methods: Forty-five patients with severe emphysema (GOLD III and IV) underwent inspiratory 3D-HRCT and contrast-enhanced MR-perfusion (1.5T; 3.5 mm × 1.9 mm × 4 mm). 3D-HRCT data was analyzed using a software for detection and visualization of emphysema. Emphysema was categorized in four clusters with different volumes and presented as overlay on the CT. CT and lung perfusion were visually analyzed for three lobes on each side using a four-point-score to grade the abnormalities on CT (1: predominantly small emphysema-clusters to 4: >75% large emphysema-clusters) and MRI (1: normal perfusion to 4: no perfusion).
Results: A total of 270 lobes were evaluated. At CT, the score was 1 for 9 lobes, 2 for 43, 3 for 77, and 4 for 141 lobes. At MRI, the score was 1 for 13 lobes, 2 for 45, 3 for 92, and 4 for 120 lobes. Matching of lung parenchymal destruction and reduced perfusion was found in 213 lobes (weighted kappa = 0.8). The score was higher on CT in 44, and higher on MRI in 13 lobes.
Conclusion: 3D-HRCT and 3D MR-perfusion show a high lobar agreement between parenchymal destruction and reduction of perfusion in patients with severe emphysema.

Keywords: Lung; Emphysema; 3D-HRCT; MR-perfusion; Lobar analysis

1. Introduction

The matching of pulmonary blood flow with ventilation is crucial for the proper function of the lung as an efficient gas exchanger. In patients with severe chronic obstructive pulmonary disease (COPD) and emphysema, ventilation is impaired due to airway obstruction and parenchymal destruction, which in turn leads to impaired perfusion due to hypoxic vasoconstriction (Euler–Liljestrand reflex) [1]. However, it is known, that the distribution of perfusion does not necessarily match morphological, emphysematous parenchymal changes [2]. Novel therapies, such as volume reduction surgery or endobronchial valve placement, try to correct this mismatch either at extraanatomical level or at a lobar or segmental level [3–6].

The gold standard for morphological evaluation of lung tissue in vivo is high-resolution computed tomography (HRCT). Analysis of emphysema is most often done by threshold based methods (density mask technique), where all voxels with hounsfield units (HU) below −950 HU (valid for thin slices) are assumed to be pure air and therefore emphysematous [7–9]. The distribution of emphysema throughout the lung is more or

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doi:10.1016/j.ejrad.2007.01.020

less heterogeneous. Currently, there is no generally accepted standard to define the heterogeneity of emphysema [10].

HRCT using 1–2 mm slice thickness with a 10–20 mm inter-slice gap is only moderately appropriate for multiplanar reconstructions and is not sufficient for advanced 3D texture analysis [11,12]. Modern multi-detector CT (MDCT) scanners allow whole lung coverage using contiguous acquisition of 1 mm thin slices reconstructed with an overlap of e.g. 20% (thin section MDCT or 3D-HRCT) [13]. This contiguous and high-resolution datasets are required for optimal segmentation of the thoracic structures. Especially precise segmentation of the tracheobronchial tree, which might be falsely counted as emphysema, is required. This image basis allows for a detailed evaluation and interpretation of the heterogeneity of emphysema. Emphysematous changes are strongly associated with a reduction of pulmonary ventilation [14]. Therefore, a 3D density mask technique can be adequately used as an indirect marker of ventilation.

The structural damage in emphysema leads to a local reduction in pulmonary blood flow [10]. Local pulmonary blood flow is usually assessed by nuclear medicine with well known restraints regarding spatial resolution and radiation exposure [15]. Thus, new MR techniques are an attractive alternative to provide volumetric perfusion 3D datasets with a high spatial resolution and the possibility for multiplanar reformation [16,17].

Earlier studies tried to assess the global ventilation/perfusion (V/Q) ratios by use of global measures like pulmonary function tests (PFT) or the multiple inert gas elimination technique [18]. To our knowledge, there is no study in the literature using 3D high-resolution techniques for assessing the regional V/Q ratios in patients with COPD.

Therefore, the goal of our study was to evaluate the agreement between parenchymal destruction as judged by advanced texture analysis based on 3D-HRCT and reduction of pulmonary perfusion using 3D MR perfusion in patients with advanced emphysema. The severity of the surrogates for ventilation and perfusion was visually scored on a lobar level. The degree of impairment was compared with pulmonary function tests.

2. Material and methods

We examined 45 (13 female, 32 male) consecutive patients (mean age 62 ± 6 years, range 43–76) suffering from severe chronic obstructive lung disease (COPD) as clinical diagnosis. Radiological diagnosis of emphysema was based on CT analysis. Body Mass Index of our study population was $25 \pm 4\,kg/m^2$ (range 18–31 kg/m^2). Patients had a smoking history of 50 ± 22 packyears (range 10–120 packyears).

The study was approved by the local ethics committee and all subjects were informed prior to the investigation. The CT examination was performed as part of routine standard work-up of the patients for tentative surgical or endobronchial treatment [3,4]. Inclusion criteria were smoking history, severe changes in lung function tests indicative for obstructive disease (GOLD III and IV) and no evidence of α_1-antitrypsin deficiency. Patients presenting with atelectasis, tumour or pneumonia on CT were not included in this evaluation. CT and MR examinations were performed on the same day, 1–2 h apart.

All patients had pulmonary function test (PFT) performed on a body plethysmograph (MasterScreen® Body, Jaeger, Germany) according to the guidelines of the European Respiratory Society [19]. Forced expiratory volume in 1 s predicted (FEV_1% predicted) was 35 ± 11% (range 17–64%). Measurement of carbon monoxide transfer factor (TLCO) was performed in 42 of 45 patients. Mean TLCO% predicted was 38 ± 22% (range 15–131%). The results of the FEV_1% predicted and TLCO was used for comparison with CT morphology and MR perfusion scores.

2.1. CT

3D-HRCT was performed using a 16-row-MDCT (Aquilion 16, Toshiba Medical System Corporation, Toshigi, Japan). The examination was done during an inspiratory breath-hold in supine position. The mean breath-hold period was 11 s (range 9–13 s) depending on individual lung size. CT acquisition parameters were: collimation 1 mm, 120 kV, 150 mAs, gantry rotation time 0.5 s, pitch 1.5, large scan field. All images were reconstructed using a high frequency reconstruction algorithm (standard lung kernel) with a slice thickness of 1 mm and a reconstruction interval of 0.8 mm. For thoracic coverage 344–507 (mean 417 ± 34) images were reconstructed. No intravenous contrast medium was administered.

2.2. Texture analysis using CT data

All images were transferred to a PC (Intel Pentium 4, 2.7 GHz, 768 MB RAM, Windows XP Prof.) via routine picture-archiving and communication system (PACS). An in-house developed software (YACTA®, Mainz, Germany) was used for texture analysis [20–22]. Briefly, the software combines different techniques for semi-automatic segmentation of the lungs like region growing, threshold- and expert-based methods, and morphological analysis. A Gaussian denoising filter was applied to all images before analysis. Only voxels segmented and marked as lung parenchyma were included in further analysis. Voxels below −950 HU were segmented as emphysema [7–9].

Thin slice MDCT allows for a 3D segmentation and volumetric evaluation of different compartments of the lung parenchyma. The emphysematous regions were further categorized according to their volume. The 3D emphysematous volumes were assigned to one of the following size classes (=clusters): 2–8 mm^3 (class 1), 8–65 mm^3 (class 2), 65–120 mm^3 (class 3) and >120 mm^3 (class 4) modified from Blechschmidt et al. [20,22]. The different clusters were color coded and presented as an overlay to the original CT images for improvement of visual assessment.

Due to the 3D nature of the datasets multiplanar reformats were possible without loss of information or need for interpolation.

2.3. MR perfusion

MR examinations were performed in supine position on a clinical 1.5 T whole-body MR scanner (Magnetom Symphony; Siemens Medical Solutions, Erlangen, Germany) offering a

Table 1
Severity scores form of CT and MR perfusion

Score	CT	MRI
1	No emphysema or few and small clusters	Normal perfusion without any defects
2	Small and intermediate clusters, cluster class 4 < 25% of the lobe	Small perfusion defects, <25% of the lobe
3	Emphysema cluster class 4; 50–75% of the lobe	Large perfusion defects, 50–75% of the lobe not perfused
4	Emphysema cluster class 4 > 75% of the lobe	Loss of perfusion >75% of the lobe

Scores were applied to three lobes on each side for each modality separately and blinded.

maximum gradient strength of 30 mT/m and a slew rate of 125 T/m/s. Two six-channel body phased array coils were placed anterior and posterior of the patients and used for signal detection. The arms of the patient were placed above the head and only in two patients beside the body (due to shoulder pain). A time-resolved contrast-enhanced 3D gradient echo pulse sequence (TREAT) with generalized autocalibrating partially parallel acquisitions (GRAPPA) was applied using the following imaging parameters: repetition time (TR) 1.9 ms; echo time (TE) 0.8 ms; flip angle 40°; receiver bandwidth 1220 Hz/pixel; acceleration factor 2; reference k-space lines for calibration 20; field of view (FOV) 480 mm × 360 mm; matrix 256 × 96; slab thickness 160 mm; 44 partitions; and scan time per 3D dataset 1.5 s [23]. In total, 20 consecutive datasets were acquired during one inspiratory breath hold in coronal orientation, starting with the beginning of the injection of contrast. Gadolinium-DTPA was injected through the antecubital vein using an automatic power injector at a rate of 5 mL/s with a dose of 0.1 mmol/kg body weight followed by a saline flush of 30 mL injected at the same injection rate.

2.4. Post processing of MR perfusion data

Due to the parallel start of image acquisition and injection of the contrast medium the first one or two datasets showed no contrast enhancement in the lung parenchyma ($Dataset_{baseline}$). By use of ROI analysis the dataset with the maximum contrast enhancement in the lung parenchyma was identified ($Dataset_{max\text{-}enhance}$). These two datasets were subtracted resulting in a $Dataset_{subtraction}$ to pronounce the T1 effect of the contrast medium reflecting lung perfusion. Afterwards, the $Dataset_{subtraction}$ was used to calculate 10 mm thick maximum intensity projections ($Dataset_{MIP}$) in coronal orientation with an increment of 8 mm, in order not to miss any perfused area. The $Dataset_{subtraction}$ and $Dataset_{MIP}$ were transferred to PACS.

2.5. Image analysis of CT morphology and MR perfusion

All datasets were evaluated in axial, coronal and sagittal orientation (multiplanar mode). Evaluation was done by two experienced chest radiologists in a consensus reading session. CT and MRI were evaluated separately and in random order. Since interventional therapies are mainly based on a lobar approach, the distribution of emphysema clusters and visual assessment of severity and perfusion pattern were analyzed for three lobes on each side (lingula was counted as a separate lobe). A four-point-score was used for evaluation of emphysema on CT (1: few and small emphysema clusters to 4: large emphysema clusters >75% of the lobe) and lung perfusion on MRI (1: normal to 4: loss of perfusion >75% of the lobe) (Table 1).

For assessment of the heterogeneity of the lung parenchymal destruction or MR perfusion a classification was used based on three categories (modified from [24]): markedly heterogeneous—two or more score points difference between lobes; intermediately heterogeneous—one score point difference between lobes; homogeneous—no difference throughout the lung. This classification was done for each lung separately.

2.6. Statistical analysis

Data handling was done using Microsoft Excel 2003 SP 1. For correlation between different results linear regression analysis was applied. For agreement between CT and MRI results weighted Kappa-Analysis was performed (MedCalc®, MedCalc Software, Version 8.1.0.0, Belgium).

3. Results

All radiological examinations were eligible for evaluation (whole lung covered, no breathing artifacts and automatic CT evaluation possible). In all cases the leading CT diagnosis was severe centrilobular emphysema with architectural destruction. No large bullae were detected.

CT and MR images were read separately. At CT and MRI 270 lobes were evaluated. Nine lobes with normal parenchymal architecture and perfusion were detected. At CT, the score was 1 for 9 lobes, 2 for 43, 3 for 77, and 4 for 141 lobes. At MRI, the score was 1 for 13 lobes, 2 for 45, 3 for 92, and 4 for 120 lobes. In 213 lobes, the score was identical for CT and MRI (weighted kappa = 0.8). For each modality the severity scores of all six

Table 2
Results of the evaluation of the CT and MR perfusion scoring

Score	CT				
	Score = 1	Score = 2	Score = 3	Score = 4	Sum
MRI					
1	9	4	0	0	13
2	0	32	13	0	45
3	0	7	58	27	92
4	0	0	6	114	120
Sum	9	43	77	141	270

The numbers refer to the quantity of scores of each modality. The weighted kappa value for the agreement between CT and MRI scores was 0.77.

Table 3
Agreement of distribution between emphysema changes on CT and perfusion impairment on MRI based on three categories (markedly heterogeneous—two or more score points in difference between lobes; intermediately heterogeneous—one score point in difference between lobes; homogeneous—no difference throughout the lung)

MR perfusion heterogeneity	CT emphysema heterogeneity			
	Markedly heterogeneous	Intermediately heterogeneous	Homogeneous	Total number
Markedly heterogeneous	16	7	0	23
Intermediately heterogeneous	3	30	10	43
Homogeneous	0	3	21	24
Total number	19	40	31	90

This classification was done for right and left lung separately.

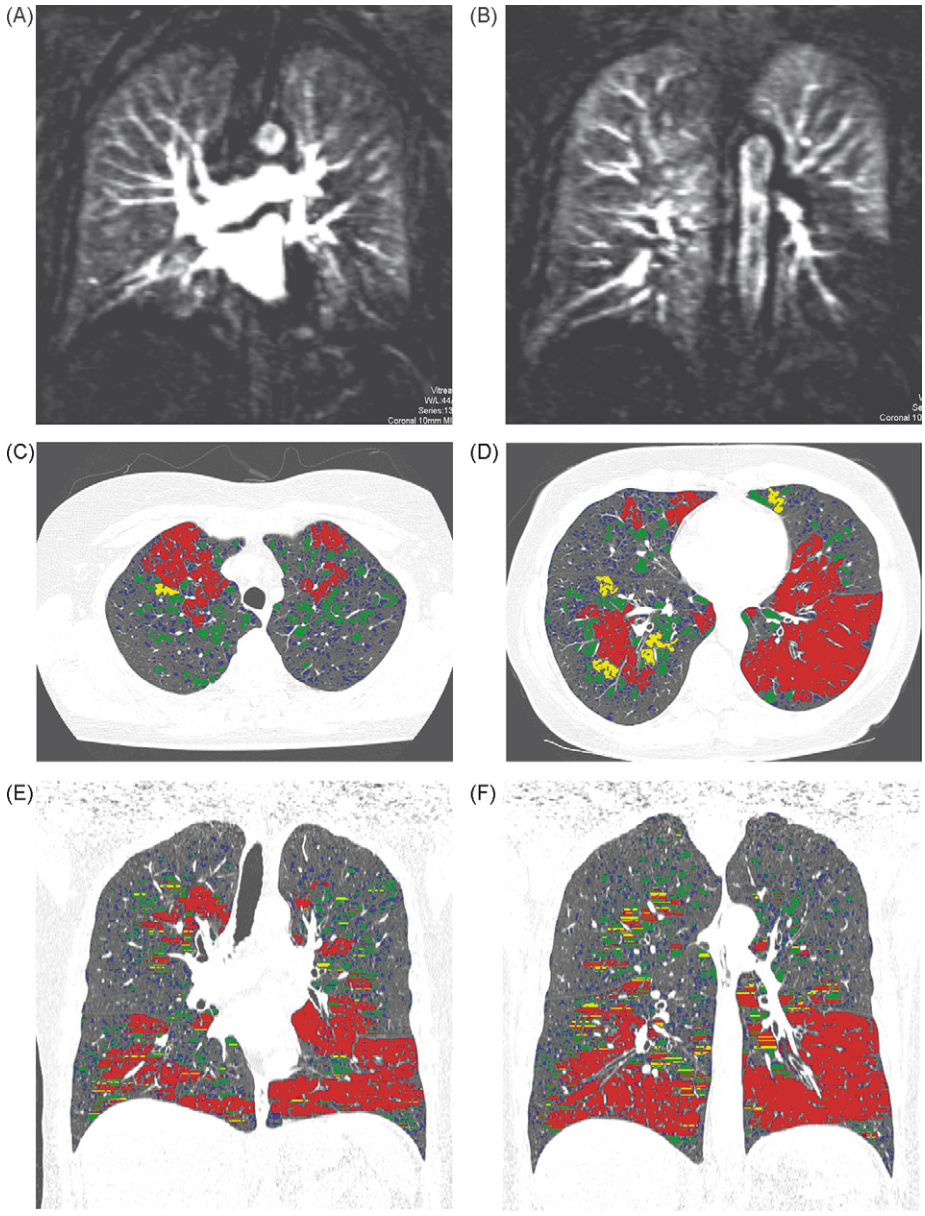

Fig. 1. Fifty-two years old female patient suffering from emphysema GOLD class 3 (FEV_1 predicted 47%) with smoking history of 40 packyears. Ten millimeters ventral and dorsal $Dataset_{MIP}$ of coronal lung perfusion MR images (A and B): the upper and middle lobe on the right were scored 1. The right lower lobe was scored 2. On the left we scored 2, 3 and 4 for upper, middle and lower lobe, respectively. Color map of two original axial CT images (C and D) and coronal images ventral and dorsal (E and F): clusters class 4 (red), class 3 (yellow), class 2 (green) and class 1 (blue). The right lung was scored 2 for each lobe. On the left we scored 2, 3 and 4 for upper lobe, lingula and lower lobe, respectively.

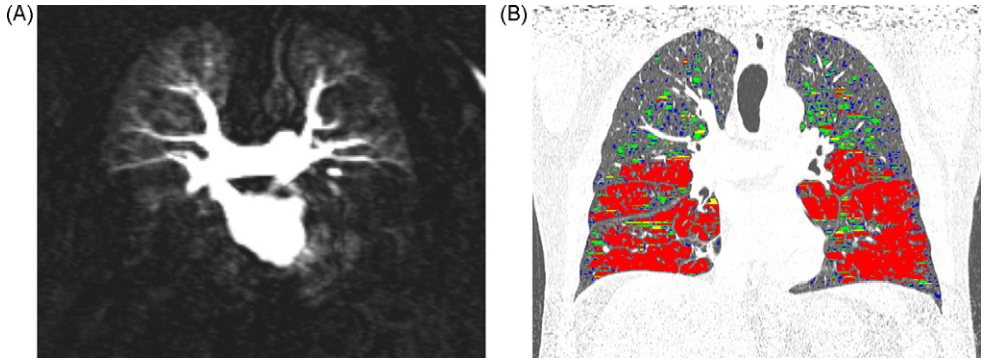

Fig. 2. Sixty years old male patient suffering from severe emphysema GOLD class 4 (FEV_1 predicted 25%) with smoking history of 48 packyears. Ten millimeters ventral and dorsal $Dataset_{MIP}$ of coronal lung perfusion MR images (A): the upper lobe was scored 1 for both lungs. The middle lobe and lingula were scored 3 for right and 4 for left lung. We scored the both lower lobes 4. Color map of coronal CT image (B): clusters class 4 (red), class 3 (yellow), class 2 (green) and class 1 (blue). The upper lobes were scored 1 and 2 and the lower lobes 3 and 4 for right and left lung, respectively. The middle lobe and lingula were scored 4 on each side.

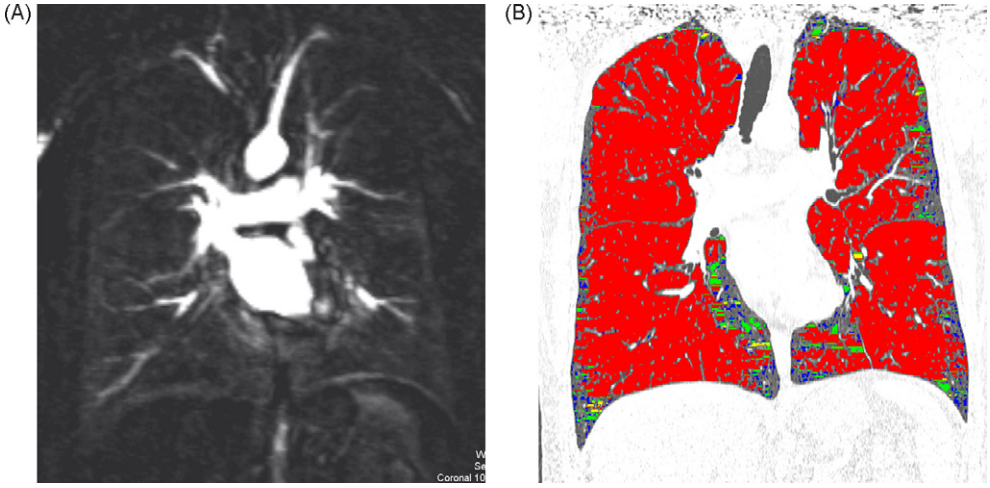

Fig. 3. Fifty years old female patient suffering from emphysema GOLD class 3 (FEV_1 predicted 37%) with smoking history of 35 packyears. Ten millimeters MIP of original coronal lung perfusion MR images (A): the upper, middle and lower lobes on each side were scored 4. Color map of coronal CT image (B): clusters class 4 (red), class 3 (yellow), class 2 (green) and class 1 (blue). The upper, middle and lower lobes on each side were scored 4.

lobes were added up to get one overall severity score. We found a high correlation between the overall severity score of CT and MRI ($R = 0.9$). The score was higher (more severe) at CT in 44, and higher at MRI in 13 lobes. These lobes showed a discrepancy of one score point and were distributed over all categories. Although MRI under-scored in slightly more patients than CT, no systematic under- or overscoring was found (Table 2).

In most patients we found a very heterogeneous distribution of emphysema (CT score) and lung perfusion (MR score) as identified by score values ranging intra-individually over three or four categories. A good level of agreement and distribution between CT and MRI heterogeneity evaluation was found (weighted kappa 0.7). Most of the patients showed an intermediate heterogeneity of perfusion and emphysema. The homogenous and markedly heterogeneous distribution categories were nearly equally distributed (Table 3).

The heterogeneity is shown for the right and left lung (Fig. 1) and for the upper and lower lung (Fig. 2). Only two patients showed a homogeneous distribution of severely reduced lung perfusion with severe parenchymal damage (Fig. 3).

We found no linear correlation between the sum of CT or MRI severity scores and FEV_1% predicted (each $R < 0.4$) or TLCO% predicted (each $R < 0.5$).

4. Discussion

A high agreement between parenchymal destruction and lung perfusion on a lobar level was confirmed in patients with emphysema in high 3D quality. A heterogeneous distribution of parenchymal destruction and perfusion was found in most patients. The severity of morphological and functional impairment showed no correlation with either the predicted FEV_1% or TLCO%.

With advances in the understanding of pulmonary emphysema, it has been become clear that emphysema tends to be complicated by diffuse abnormalities in the pulmonary peripheral microvasculature. Radionuclide perfusion scintigraphy (e.g. using ^{99}mTc-macro-aggregated human albumin) can be used to assess these abnormalities, but it has substantial limitations with respect to spatial and temporal resolution [25,26]. Advanced 3D

imaging using CT and MRI facilitates the assessment of the local agreement of ventilation and perfusion.

Gas exchange in the lungs is maintained by a local match between ventilation and perfusion. The structural loss of lung parenchyma in emphysema leads to a significant increase of closed volume and a decreased ventilation of those regions [14] with subsequent hypoxic vasoconstriction [1]. The loss of pulmonary arteries is related to the severity of parenchymal destruction and the mechanical compression of pulmonary arteries in case of hyperinflation [27,28].

HRCT is an established method for the non-invasive detection of pulmonary emphysema [7,29]. CT datasets can either be evaluated by visual scoring or computer-assisted quantification. The visual assessment allows for grading severity on any anatomical level, however, systemic overestimation and only moderate interobserver agreement compromises the utility of subjective visual grading of emphysema [30]. It was suggested to combine the subjective visual and objective grading methods [31,32]. With this in mind we performed an advanced quantitative analysis of structural CT characteristics. The severity of structural destruction was color coded to support the visual assessment of emphysema. Consensus reading by two experienced chest radiologist further reduced the influence of subjective grading.

Emphysema due to COPD is a heterogeneous disease affecting all parts of the lung with differing severity. Therefore, it is important to evaluate the whole lung, especially if the dataset is intended to be used for treatment monitoring and follow-up. This became possible with MDCT scanner technology, facilitating a 3D approach of HRCT. This approach was used in this study by the visual grading of the severity of the parenchymal destruction. We found a broad spectrum of scores, i.e. 3 of 4 categories in most patients.

As stated above the emphysematous destruction is associated with a reduction in perfusion and pulmonary capillary blood volume [33]. Earlier studies evaluated the perfusion pattern in patients with emphysema using perfusion scintigraphy. This technique has two major disadvantages, in that it involves radiation and provides low spatial resolution. However, the combined information from CT and lung perfusion scintigraphy was superior in assessing heterogeneity of emphysema compared to CT alone [10]. A superior technique is SPECT, which is rarely used as it is very time consuming and not routinely applied for lung imaging. In a recent study no correlation was found between grading on CT and grading of pulmonary blood flow in SPECT [34]. A new, emerging technique for visualization of pulmonary perfusion is MRI [16,17,35]. With the increase in spatial resolution analysis of pulmonary perfusion and precise anatomical localization of the perfusion defects can be achieved thereby allowing for lobar analysis.

In another study a reduction of perfusion was not always directly associated with the severity of the structural loss of lung parenchyma [24]. In our patients with severe structural destruction a high agreement between CT morphology and MR perfusion was found. In case of discrepancies only a difference of one category was found with CT being more likely to give with a higher score than MRI (CT score was higher in 16% and MRI score was higher in 5% of the lobes).

In-depth evaluation of the relationship between changes in 3D lung morphology and perfusion that allows for detailed assessment of heterogeneity has not been published before. We found a heterogeneous but widely corresponding distribution (weighted kappa 0.7) of morphological changes and perfusion impairment. However, the discrepant areas might be the important and deserve a closer look.

From other studies it is assumed, that lung areas with better perfusion will also be better ventilated by collateral ventilation through opened acinar fenestrations (pores of Kohn) [2,36]. It was shown, that in emphysematous patients the collateral ventilation was increased by a factor of ten compared to normal volunteers. However, the ventilation was still four times less than in areas showing normal ventilation [36]. This physiological redistribution of ventilation prevents a more pronounced V/Q mismatch.

In a study with 10 patients suffering from moderate to severe COPD, 6 out of 25 examined lung regions also showed low V/Q regions with normal or almost normal blood flow. Bronchial narrowing or obstruction was suggested to be the predominant cause of the abnormal local gas exchange while the patients continued to perfuse poorly ventilated regions with a relative lack of vascular compensation [15].

Overall, the amount of V/Q heterogeneity in our study supports the idea that even in severe COPD patients regions in a borderline stage can be identified which might be amenable to intensified inhalative or intravenous therapy. This suggests that high spatial resolution techniques like 3D-HRCT and 3D MR perfusion are important although their ability to demonstrate the efficacy of therapeutical intervention needs to be further elucidated.

Global, clinical parameters like FEV_1 present an overall measure of small and large airway pathologies. In patients with severe emphysema the large airways such as the trachea are also significantly affected [37]. The severity of small airway changes and parenchymal loss showed correlations with results from pulmonary function tests [38]. However, in the majority of publications the parenchymal alterations did not correlate with the indices of exercise tolerance and pulmonary function tests [34]. While the FEV1 maneuver is patient dependent, the assessment of TLCO is not. Furthermore, the reduction of the CO diffusion capacity correlated significantly with the severity of airway obstruction and severity of emphysema scored pathologically or radiographically with CT scan examinations [39]. In our study the severity grading of emphysema, based on loss of structure and perfusion, showed no correlation with FEV_1% predicted and poor correlation with TLCO% predicted. This is not surprising since the TLCO measurement is more reliable in homogeneous ventilation of the lung [40], which obviously was not the case in our patients as in other studies [41–43].

Local assessment of V/Q might already identify disease at early stages with better therapeutic options and a higher quality of life. For this purpose, high resolution 3D techniques are mandatory to allow differentiation between perfusion deficits and ventilation abnormalities.

At least two limitations to our study have to be mentioned. Firstly, only patients with severe disease were included.

Thus, the transfer of the findings to patients with moderate or mild emphysema warrants confirmation. To further improve the clinical impact of the knowledge of local structural loss and functional impairment additional dynamic aspects should be examined e.g. assessment of ventilation and perfusion in expiration. Secondly, only the parenchymal destruction was visually enhanced by segmentation and color coding. A way to pronounce the presence or absence of lung perfusion would be to color code the perfusion studies too. Unfortunately this was not possible in the present study. Also matching or subtraction of MR perfusion and 3D-HRCT was not possible.

In conclusion we could confirm a strong link between structural destruction of the lung parenchyma and the local perfusion in patients with severe emphysema. A broad spectrum from a homogeneous to a markedly heterogeneous distribution of emphysema on 3D-HRCT and perfusion impairment on MR perfusion was found. However, on a lobar level both distribution patterns were not necessarily in concordance. Nowadays this information can be achieved using state-of-the-art 3D visualization of parenchymal destruction and MR perfusion with higher resolution than before to demonstrate the individual relation between pulmonary structure and function.

Acknowledgement

This work was supported by the German National Research Agency (DFG): “Image-based V/Q analysis” (FOR 474-2).

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