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Quantitative and Semi-quantitative Measures of Regional Pulmonary Parenchymal Perfusion by Magnetic Resonance Imaging and their Relationships to Global Lung Perfusion and Lung Diffusing Capacity – The MESA COPD Study

Katja Hueper^{1,2}, Megha Parikh³, Martin R. Prince³, Christian Schoenfeld², Chia Liu¹, David A Bluemke⁴, Stephen M Dashnaw³, Thomas A. Goldstein⁵, Eric Hoffman⁶, Joao A Lima¹, Jan Skrok¹, Jie Zheng⁷, R. Graham Barr³, and Jens Vogel-Claussen^{1,2}

¹Johns Hopkins University, Baltimore, MD

²Hannover Medical School, Hannover, Germany

³Columbia University Medical Center, New York, NY

⁴Radiology and Imaging Sciences, National Institutes of Health, Bethesda, MD

⁵Stanford University, Stanford, CA

⁶University of Iowa Carver College of Medicine, Iowa City, IO

⁷Washington University School of Medicine, St Louis, Missouri

Abstract

Objectives—To evaluate quantitative and semi-quantitative measures of regional pulmonary parenchymal perfusion in patients with COPD in relationship to global lung perfusion (GLP) and lung diffusing capacity (DL_{CO}).

Materials and Methods—One hundred and forty three participants in the MESA COPD Study were examined by dynamic contrast-enhanced pulmonary perfusion MRI at 1.5 T. Pulmonary blood flow (PBF) was calculated on a pixel-by-pixel basis by using a dual-bolus technique and the Fermi function model. Semi-quantitative parameters for regional lung perfusion were calculated from signal-intensity time curves in the lung parenchyma. Intra- and inter-observer coefficients of variation (CV) and correlations between quantitative and semi-quantitative MRI parameters and with GLP and DL_{CO} were determined.

Results—Quantitative and semi-quantitative parameters of pulmonary parenchymal perfusion were reproducible with CVs for all <10%. Furthermore, these MRI parameters were correlated with GLP and DL_{CO} and there was good agreement between PBF and GLP. Quantitative and semi-quantitative MRI parameters were closely correlated (e.g., $r=0.86$ for maximum signal increase with PBF). In participants without COPD, the physiological distribution of pulmonary perfusion could be determined by regional MRI measurements.

Conclusion—Regional pulmonary parenchymal perfusion can reliably be quantified from dynamic contrast-enhanced MRI. MRI-derived quantitative and semi-quantitative perfusion measures correlate with GLP and DL_{CO}.

Keywords

Pulmonary perfusion; chronic obstructive pulmonary disease (COPD); dynamic contrast-enhanced MRI; quantitative perfusion maps; diffusing lung capacity

INTRODUCTION

In chronic obstructive pulmonary disease (COPD) and emphysema, impairment of gas exchange and perfusion as well as alterations of the distribution of perfusion are important features [1–3]. Reliable, non-invasive imaging techniques that accurately quantify and monitor regional lung perfusion may provide important insights into the pathophysiology, treatment and prognosis of these diseases.

Lung perfusion can be evaluated by single-photon emission computed tomography (SPECT) [4] and absolute quantification of pulmonary blood flow (PBF) has been established and validated using positron emission tomography (PET) [5–7]. Both techniques, however, are limited by poor temporal and spatial resolution and involve radiation exposure, which limits their repeat use in clinical trials. Dynamic contrast-enhanced magnetic resonance imaging (MRI) may overcome those limitations.

Several approaches for quantification of regional pulmonary perfusion by MRI have been proposed [8–11]. They are based on the indicator dilution theory [12], which applies to blood pool contrast agents. A linear relationship between the contrast concentration in the blood pool and the MRI signal intensity is essential for the accurate quantification of pulmonary perfusion. Nikolaou et al. demonstrated that this linear relationship is maintained up to a contrast dose of 0.05 mmol/kg bodyweight gadodiamide [10], while others suggest lower contrast doses <0.036 mmol/kg bodyweight using the 3D dynamic gradient-echo fast low-angle shot (FLASH) and the dynamic 3D spoiled gradient-echo (GRE) MRI sequence, respectively, at 1.5 Tesla (T) [13]. Also dual-bolus techniques, where the arterial input function (AIF) is obtained from a prebolus scan at a lower contrast dose, have been successfully applied for quantification of lung perfusion [11, 14].

Regional semi-quantitative parameters of lung perfusion provide an alternative to absolute quantification of regional lung perfusion by MRI. They are calculated from signal intensity-time curves of the lung parenchyma and do not require a specific MRI protocol and dedicated deconvolution software. In the present study we compare quantitative and semi-quantitative measures of regional pulmonary parenchymal perfusion by MRI in a cohort of patients with COPD and controls, to determine their reliability, and to compare them to GLP as independent reference marker. Furthermore, MRI-derived regional lung tissue perfusion parameters are compared to diffusing lung capacity (DL_{CO}), an important physiological parameter of gas exchange in COPD.

MATERIALS AND METHODS

Study participants

The Multiethnic Study of Atherosclerosis (MESA) COPD Study enrolled cases of COPD and controls from two prospective cohort studies who were age 50–79 years old, had smoked 10 or more pack-years, and who did not have clinical cardiovascular disease, state IIIb–V kidney disease, asthma prior to age 45 years, prior lung resection, cancer, allergy to gadolinium, claustrophobia, weight >300 lbs, metal in the body or pregnancy. We selected all eligible participants in the MESA Lung Study [15] and oversampled participants with COPD or emphysema from the remainder of the MESA Study [16] and from the EMCAP

Study [17], in addition to a small number from neither study. The current report is restricted to participants with quantitative measures of PBF, who were all recruited at one site (XX). Eighty COPD patients and 63 participants without COPD were included. The protocol was approved by the institutional review boards of all collaborating institutions.

Pulmonary parenchymal perfusion MRI

Between 2008 and 2011 pulmonary and cardiac MRI were performed on a 1.5 T whole-body MRI system (Signa LX, GE Healthcare, Waukesha, Wisconsin) using a phased-array coil.

For pulmonary perfusion measurements, coronal 3D spoiled gradient echo imaging using the TRICKS (Time Resolved Imaging of Contrast Kinetics) sequence was acquired in full inspiration. This sequence allows measurement of first-pass contrast kinetics with high temporal and spatial resolution. The following parameters were used: TR/TE/flip angle = 2.5/0.8/30°, parallel imaging acceleration factor = 2, matrix 256×128, field of view (FOV) = 480 mm, slice thickness = 10 mm reconstructed at 5 mm intervals (i.e. 50% slice-overlap) using zero filling interpolation, 28–44 slices (depending on the thoracic anterior to posterior dimension), scan time = 60 s. A bolus of 0.1 mmol/kg bodyweight Gd-DTPA (Magnevist, Berlex, Wayne, New Jersey) was injected at 5 ml/s, followed by a saline flush of 20 ml at the same injection rate. With this technique, first-pass pulmonary perfusion was imaged with an image update rate of 1.2–1.8 s.

The AIF for absolute quantification of PBF, was derived from a first-pass contrast bolus injection with a region of interest (ROI) in the right ventricle on a short-axis slice: After injection of 0.05 mmol/kg bodyweight Gd-DTPA at 5 ml/s an ECG-gated multi-phase fast gradient-recalled echo train sequence with a one R to R wave temporal resolution was acquired: TR/TE = 6.4/1.3 ms, inversion time = 176 ms, flip angle = 25°, echo train length = 4, matrix = 192×128, FOV = 380 mm, slice thickness = 8 mm with a 5 mm gap between slices, number of slices 3, phases reconstructed per slice = 40.

Quantitative and semi-quantitative parameters of pulmonary parenchymal perfusion

Three representative coronal slices of the lung were analyzed: one central slice at the level of the tracheal bifurcation, one posterior and one anterior slice each at half distance between the central slice and the posterior or the anterior chest wall, respectively. Quantitative and semi-quantitative perfusion analysis was performed using the software Perfusion Imaging Toolkit [18]. Image noise was decreased by temporal and spatial wavelet denoising. A baseline correction was performed for quantitative and semi-quantitative analysis [19].

PBF was calculated on a pixel-by-pixel basis using signal intensity-time curves of the lung parenchyma (TRICKS sequence) and the right-ventricular cavity (AIF). As the contrast dose for the AIF was lower than the dose for the pulmonary perfusion scan, the signal intensities of the AIF-curve, were multiplied by the ratio between the injection quantities for the pulmonary perfusion bolus and for the AIF pre-bolus after baseline correction. Afterwards PBF was calculated by deconvolution that assumes a Fermi-function model as the residuum. The parameters of this Fermi model were fitted using the Marquart-Levenberg curve fitting algorithm [19–21]. A γ -variate function was fitted to signal intensity-time curves in the lung parenchyma. Mean transit time (MTT) was calculated as the first moment of this γ -variate function as described by Tomasian et al. [9] and was displayed in parameter maps. Regions of interest (ROI) were drawn on subtracted perfusion images including the peripheral ~2 cm of the lung and excluding large vessels. These ROIs were copied to quantitative maps of PBF and MTT. Mean values for the posterior, central and anterior slice were recorded (Fig. 1). Mean pulmonary blood volume (PBV) was calculated according to the central volume principle [12]: $PBV = PBF \cdot MTT$.

In order to determine semi-quantitative parameters of pulmonary parenchymal perfusion a γ -variate function was fitted to the signal intensity-time curve of the lung parenchyma. Only the first-pass of the contrast kinetic was used for this analysis. The following parameters were measured in lung regions corresponding to the quantitative parameters: maximum signal increase (SI) is the difference between maximum and 20% signal intensities of the γ -variate function, upslope is the maximum signal increase per time interval, time to peak (TTP) is the time difference between 20% and maximum signal intensities of the curve and full width half maximum (FWHM) is the time difference between 50% signal intensities (Fig. 2).

Intra- and inter-reader replicate measures were performed for 20 randomly chosen patients with COPD and controls. Two readers who were blinded in terms of the case status and the percent emphysema independently analyzed these cases. One of the readers re-analyzed the MRI scans after approximately 2 months for the second time, blinded to the results of the first read.

Global lung perfusion

GLP was calculated as previously described by Oechsner et al. [14]. Cardiac output was determined from phase-contrast flow measurements in the main pulmonary artery using QFlow software (Medis, Leiden, The Netherlands). A retrospectively ECG-gated fast 2D phase-contrast sequence was used for flow quantification: TR/TE = 6.2 ms/minimum, flip angle = 20°, matrix = 256×128, FOV = 350 mm, slice thickness = 5 mm, VENC = 100 cm/s, temporal resolution = 30 ms, reconstructed phases = 30. GLP was calculated as cardiac output divided by total lung capacity (TLC) measured by body plethysmography.

Pulmonary function

Pulmonary function was measured in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [22–24]. Pre- and post-bronchodilator spirometry was performed for all participants using a rolling-barrel spirometry following a standardized protocol with central over-reading, as previously described [25]. Single-breath DL_{co} was measured with a Sensormedics Autobox 220 Series instrument (Viasys Healthcare, Yorba Linda, CA). Breath-hold time was assessed by the method of Jones and Meade [26]. Body plethysmography was performed using a V6200 Series Autobox (Sensormedics, Yorba Linda, CA).

Predicted spirometry values were calculated using Hankinson equations [27] and lung volumes were calculated from Crapo questions for participants under 65 years and Garcia-Rio equations for participants 65 years and older [28, 29]. COPD was defined following ATS/ERS and Global Initiative for Chronic Lung Disease guidelines as a post-bronchodilator FEV₁/FVC ratio <0.70 [30, 31].

Statistical analysis

For the main analysis of reliability and correlations of MRI perfusion parameters, perfusion values of the middle slice were averaged over both lungs. The reliability of quantitative and semi-quantitative MRI parameters was assessed by determination of intra- and inter-observer coefficients of variation (CV). The relationship between quantitative and semi-quantitative MRI parameters and with GLP, percent predicted DL_{CO} and DL_{CO}/VA was determined using Pearson's coefficient of correlation and linear regression. The agreement of GLP and PBF was assessed using Bland-Altman methods [32] for all participants as well as separately for COPD patients and controls. GLP and PBF were compared using a paired t-test. Regional differences of pulmonary parenchymal perfusion were evaluated in subjects without COPD (n=63) by comparing perfusion values between left and right, posterior and

anterior and superior and inferior lung using paired t-tests. P-values of <0.05 were considered statistically significant.

RESULTS

The characteristics of the 143 participants in the MESA COPD Study with quantitative pulmonary parenchymal perfusions measures are summarized in Table 1. All participants had smoked ≥ 10 pack years and 68% smoked at the time of inclusion. Mean FEV₁ was $84.6 \pm 23.6\%$ predicted, mean FEV₁/FVC ratio was 0.65 ± 0.14 and DL_{CO} was $59.0 \pm 15.6\%$ predicted.

GLP was available in $n=74$ participants, because TLC and MRI flow measurements, which are both necessary for calculation of GLP, were only available for these participants. The semi-quantitative parameters TTP and FWHM could not be determined in $n=1$ and $n=9$ subjects, respectively, because the profile of the signal intensity-time curve was not a good gamma variate fit. The number of participants included in each analysis is given in Figure 3.

Reliability of quantitative and semi-quantitative measures of pulmonary parenchymal perfusion by MRI

All quantitative and semi-quantitative measures of pulmonary parenchymal perfusion by MRI had intra- and inter-observer CVs below 10% (Table 2). For example, CVs of PBF were 6.8% for intra- and 7.6% for inter-observer variability. The inter-observer CVs for semi-quantitative measures were similar whereas the intra-observer CVs for semi-quantitative measures were lower.

Comparison of quantitative and semi-quantitative measures of pulmonary parenchymal perfusion by MRI

Mean PBF of all participants was 65.5 ± 42.5 ml_{blood} per min and 100ml_{lung}, mean PBV was 4.33 ± 2.61 ml_{blood} per 100ml_{lung} and MTT was 4.42 ± 1.54 s. SI correlated well with PBF ($r=0.86$; $P<0.001$), as did upslope, without major outliers (Figure 4). MTT negatively correlated with semi-quantitative parameters. All quantitative and semi-quantitative measures of pulmonary parenchymal perfusion were correlated (Table 3).

Quantitative and semi-quantitative measures of pulmonary parenchymal perfusion by MRI and GLP and DL_{CO}

Calculated mean GLP was 85.8 ± 20.5 ml_{blood} per min and 100ml_{lung} in 74 participants with available measures. In those 74 participants, MRI-derived mean PBF for the central coronal slice was associated with GLP ($r=0.42$, $P<0.001$). Mean PBF in this slice - as a parameter of regional parenchymal perfusion - was lower than GLP (mean difference PBF-GLP = -14.6 ml_{blood} per min and 100ml_{lung}; 95% CI -24.1 , -5.2 ; $P=0.003$); however, this difference varied by COPD status ($P=0.001$). There was good agreement between PBF and GLP in controls without COPD ($n=26$; mean difference PBF-GLP = 5.5 ml_{blood} per min and 100ml_{lung}; 95% CI -12.9 , 23.9 ; $P=0.54$; Figure 5a). In contrast, among COPD patients, there was a significant difference between GLP and PBF ($n=48$; mean difference PBF-GLP = -25.5 ml_{blood} per min and 100ml_{lung}; 95% CI -35.3 , -15.8 ; $P<0.001$; Figure 5b).

Semi-quantitative measures of pulmonary perfusion also correlated with GLP (Table 4), with the strongest correlation being exhibited for SI. PBF, SI and upslope showed significant positive correlations with percent predicted DL_{CO} and DL_{CO}/VA, MTT negatively correlated with these parameters of lung function (Table 4).

Regional distribution of pulmonary parenchymal perfusion among participants without COPD or emphysema

Among 63 controls without COPD, PBF and PBV in the dependent posterior lung parenchyma were significantly higher when compared to the non-dependent anterior lung parenchyma ($P<0.001$), whereas MTT was significantly shorter in the posterior lung ($P<0.001$). Correspondingly, regional differences of semi-quantitative measures were observed in gravitational direction (posterior vs anterior). In cranio-caudal direction on the central coronal slice, PBF and PBV were higher in superior than in inferior lung regions (Table 5).

DISCUSSION

Our results demonstrate that regional pulmonary parenchymal perfusion can reliably be quantified in patients with COPD and controls using dynamic contrast-enhanced MRI and the Fermi function model. In a large cohort of COPD patients and healthy controls, semi-quantitative and quantitative perfusion parameters correlated with GLP and DL_{CO} , and quantitative perfusion measures were in agreement with GLP.

Absolute quantification of pulmonary parenchymal perfusion is challenging and time-consuming and requires specific imaging and contrast protocols as well as dedicated post-processing software [21, 33]. A close correlation between quantitative and semi-quantitative MRI parameters of pulmonary perfusion was observed in this study. This indicates, that semi-quantitative measures, that can be calculated quickly and reliably from signal intensity-time curves of the lung parenchyma, may be useful as surrogate markers for regional PBF.

For the main analyses of pulmonary parenchymal perfusion, only the middle MRI slice was used due to its higher reliability compared to other locations. The posterior and anterior locations were occasionally affected by atelectasis and cardiac motion, respectively. Overall, mean quantitative perfusion values in this study were comparable with values of other studies investigating pulmonary parenchymal perfusion by dynamic contrast-enhanced MRI or PET imaging. For example, in a study of Ohno et al. mean PBF was 122.5 ± 25.6 ml_{blood} per min and 100ml_{lung}, PBV 9.7 ± 4.3 ml_{blood} per 100ml_{lung} and MTT 4.7 ± 1.7 s in healthy controls. In the same study perfusion values of $n=13$ COPD patients were lower than in controls with PBF = 65.6 ± 46.9 ml_{blood} per min and 100ml_{lung}, PBV = 4.1 ± 5.7 ml_{blood} per 100ml_{lung} and MTT = 3.7 ± 3.2 s [8]. PET imaging with ^{15}O -water in $n=15$ healthy controls revealed mean PBF of 121 ± 32 ml_{blood} per min and 100ml_{lung} [7].

According to Oechsner et al. GLP was calculated as a contrast agent-independent reference to PBF [14]. Mean GLP was significantly higher than MRI-derived PBF of the central slice in the full sample; however this difference varied by case status. In control subject without COPD, the agreement between PBF and GLP was good and no significant difference was observed. The discrepancy in the agreement in controls and COPD participants may be explained by regional perfusion variation according to the severity and distribution of emphysema in COPD patients. Furthermore, this important finding suggests that regional quantification of pulmonary parenchymal perfusion is essential in COPD patients. We also observed good correlation of MRI perfusion parameters with DL_{CO} indicating that pulmonary perfusion was relevant for effective gas exchange.

Measurement of regional pulmonary parenchymal perfusion by MRI enabled the depiction of the physiological distribution of lung perfusion in participants without lung disease. In accordance with previous studies, PBF, PBV, SI and upslope in the posterior dependent lung were significantly higher than in the anterior non-dependent lung and, inversely, MTT was significantly shorter in the posterior than in the anterior lung parenchyma [7, 8, 33]. For

example, by MRI measurement Ohno et al. found comparable significant regional PBF differences of $148.1 \pm 17.3 \text{ ml}_{\text{blood}} \text{ per min}$ and $100 \text{ ml}_{\text{lung}}$ in the posterior and $97.6 \pm 13.7 \text{ ml}_{\text{blood}} \text{ per min}$ and $100 \text{ ml}_{\text{lung}}$ in the anterior lung parenchyma [8]. Similar to Hansch et al., PBF and PBV were higher in the superior than in the inferior lung [33]. Due to the bell-shape of the lungs the apical part of the lung on a central coronal slice is relatively close to the posterior chest wall. Therefore, some gravitational effects may occur in the lung apex, which explain observed higher perfusion values in the superior than in the inferior part of the lung in patients lying supine.

We used a dose of 0.1 mmol/kg of Gd-DTPA to achieve sufficient contrast to noise in the pulmonary parenchyma. However, at this dose the relationship between contrast concentration and signal intensity for the AIF in the main pulmonary artery is not linear [10]. Therefore we used a lower contrast dose of 0.05 mmol/kg bodyweight with higher temporal resolution and ECG gating for the AIF. Using a different gradient echo sequence for the AIF likely introduces a systematic error. As the MRI sequence protocol is the same for all patients, we have the same systematic error for all patients in this study. Nonetheless, our quantitative MRI parameters are in good agreement with GLP in healthy control subjects. Also, values of PBF and regional distribution of perfusion within the lung parenchyma are in the same range as reported in prior MRI and PET studies [7, 8]. Thus, we believe that our MRI sequence protocol has a systematic error, which does not impair the overall results and conclusion of our work. Another limitation is the use of an extravascular MRI contrast agent, so that applying the indicator dilution theory may cause difficulties [34]. However, most studies use extravascular contrast agents and achieve comparable results with perfusion measures derived from PET imaging or MRI with blood pool contrast agents [6, 7, 33].

In conclusion, regional pulmonary parenchymal perfusion can reliably be quantified from dynamic contrast-enhanced MRI using the Fermi function model. MRI derived quantitative and semi-quantitative perfusion measures correlated with each other and with GLP and DL_{CO} . Due to close correlation of quantitative and semi-quantitative parameters, semi-quantitative values may be useful as surrogate markers for regional PBF in clinical practice and for follow-up examinations.

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LITERATURE

1. Zanini A, Chetta A, Imperatori AS, et al. The role of the bronchial microvasculature in the airway remodelling in asthma and COPD. *Respir Res.* 2010; 11:132. [PubMed: 20920222]
2. Ley-Zaporozhan J, Ley S, Kauczor HU. Proton MRI in COPD. *COPD.* 2007; 4:55–65. [PubMed: 17364678]
3. Santos S, Peinado VI, Ramirez J, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *Eur Respir J.* 2002; 19:632–8. [PubMed: 11998991]

4. Jogi J, Ekberg M, Jonson B, et al. Ventilation/perfusion SPECT in chronic obstructive pulmonary disease: an evaluation by reference to symptoms, spirometric lung function and emphysema, as assessed with HRCT. *Eur J Nucl Med Mol Imaging*. 2011; 38:1344–52. [PubMed: 21365251]
5. Musch G, Layfield JD, Harris RS, et al. Topographical distribution of pulmonary perfusion and ventilation, assessed by PET in supine and prone humans. *J Appl Physiol*. 2002; 93:1841–51. [PubMed: 12381773]
6. Mintun MA, Ter-Pogossian MM, Green MA, et al. Quantitative measurement of regional pulmonary blood flow with positron emission tomography. *J Appl Physiol*. 1986; 60:317–26. [PubMed: 3484739]
7. Schuster DP, Kaplan JD, Gauvain K, et al. Measurement of regional pulmonary blood flow with PET. *J Nucl Med*. 1995; 36:371–7. [PubMed: 7884497]
8. Ohno Y, Hatabu H, Murase K, et al. Quantitative assessment of regional pulmonary perfusion in the entire lung using three-dimensional ultrafast dynamic contrast-enhanced magnetic resonance imaging: Preliminary experience in 40 subjects. *J Magn Reson Imaging*. 2004; 20:353–65. [PubMed: 15332240]
9. Tomasian A, Krishnam MS, Lohan DG, et al. Adult Tetralogy of Fallot: quantitative assessment of pulmonary perfusion with time-resolved three dimensional magnetic resonance angiography. *Invest Radiol*. 2009; 44:31–7. [PubMed: 18923332]
10. Nikolaou K, Schoenberg SO, Brix G, et al. Quantification of pulmonary blood flow and volume in healthy volunteers by dynamic contrast-enhanced magnetic resonance imaging using a parallel imaging technique. *Invest Radiol*. 2004; 39:537–45. [PubMed: 15308936]
11. Risse F, Semmler W, Kauczor HU, et al. Dual-bolus approach to quantitative measurement of pulmonary perfusion by contrast-enhanced MRI. *J Magn Reson Imaging*. 2006; 24:1284–90. [PubMed: 17051533]
12. Meier P, Zierler KL. On the theory of the indicator-dilution method for measurement of blood flow and volume. *J Appl Physiol*. 1954; 6:731–44. [PubMed: 13174454]
13. Ohno Y, Murase K, Higashino T, et al. Assessment of bolus injection protocol with appropriate concentration for quantitative assessment of pulmonary perfusion by dynamic contrast-enhanced MR imaging. *J Magn Reson Imaging*. 2007; 25:55–65. [PubMed: 17152051]
14. Oechsner M, Muhlhausler M, Ritter CO, et al. Quantitative contrast-enhanced perfusion measurements of the human lung using the prebolus approach. *J Magn Reson Imaging*. 2009; 30:104–11. [PubMed: 19557852]
15. Rodriguez J, Jiang R, Johnson WC, et al. The association of pipe and cigar use with cotinine levels, lung function, and airflow obstruction: a cross-sectional study. *Annals of internal medicine*. 2010; 152:201–10. [PubMed: 20157134]
16. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol*. 2002; 156:871–81. [PubMed: 12397006]
17. Barr RG, Mesia-Vela S, Austin JH, et al. Impaired flow-mediated dilation is associated with low pulmonary function and emphysema in ex-smokers: the Emphysema and Cancer Action Project (EMCAP) Study. *Am J Respir Crit Care Med*. 2007; 176:1200–7. [PubMed: 17761614]
18. Perfusion Imaging Toolkit. 2012. http://www.stanford.edu/~tagoldst/Tom_Goldstein/Perfusion_Imaging.html
19. Goldstein TA, Zhang H, Misselwitz B, et al. Improvement of quantification of myocardial first-pass perfusion mapping: a temporal and spatial wavelet denoising method. *Magn Reson Med*. 2006; 56:439–45. [PubMed: 16791863]
20. Jerosch-Herold M, Wilke N, Stillman AE. Magnetic resonance quantification of the myocardial perfusion reserve with a Fermi function model for constrained deconvolution. *Med Phys*. 1998; 25:73–84. [PubMed: 9472829]
21. Goldstein TA, Jerosch-Herold M, Misselwitz B, et al. Fast mapping of myocardial blood flow with MR first-pass perfusion imaging. *Magn Reson Med*. 2008; 59:1394–400. [PubMed: 18421680]
22. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005; 26:720–35. [PubMed: 16204605]
23. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005; 26:319–38. [PubMed: 16055882]

24. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J*. 2005; 26:511–22. [PubMed: 16135736]
25. Hankinson JL, Kawut SM, Shahar E, et al. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. *Chest*. 2010; 137:138–45. [PubMed: 19741060]
26. Jones RS, Meade F. A theoretical and experimental analysis of anomalies in the estimation of pulmonary diffusing capacity by the single breath method. *Q J Exp Physiol Cogn Med Sci*. 1961; 46:131–43. [PubMed: 13790588]
27. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999; 159:179–87. [PubMed: 9872837]
28. Crapo RO, Morris AH, Clayton PD, et al. Lung volumes in healthy nonsmoking adults. *Bull Eur Physiopathol Respir*. 1982; 18:419–25. [PubMed: 7074238]
29. Garcia-Rio F, Dorgham A, Pino JM, et al. Lung volume reference values for women and men 65 to 85 years of age. *Am J Respir Crit Care Med*. 2009; 180:1083–91. [PubMed: 19745204]
30. Global. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease - Revised 2011. 2011.
31. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004; 23:932–46. [PubMed: 15219010]
32. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Statistical methods in medical research*. 1999; 8:135–60. [PubMed: 10501650]
33. Hansch A, Kohlmann P, Hinneburg U, et al. Quantitative evaluation of MR perfusion imaging using blood pool contrast agent in subjects without pulmonary diseases and in patients with pulmonary embolism. *European radiology*. 2012
34. Weisskoff RM, Chesler D, Boxerman JL, et al. Pitfalls in MR measurement of tissue blood flow with intravascular tracers: which mean transit time? *Magn Reson Med*. 1993; 29:553–8. [PubMed: 8464373]

Figure 1. Quantitative maps of pulmonary parenchymal perfusion at MRI and placement of ROIs in a control subject

Corresponding central slices of subtracted signal intensity TRICKS image of pulmonary perfusion (a), pulmonary blood flow (PBF) map (b) and mean transit time (MTT) map (c). ROIs were placed on subtracted signal intensity images to cover the lung periphery while excluding greater vessels and were copied to parameter maps. PBF and MTT maps show homogeneous distribution of perfusion in this participant without COPD. Mean PBF in this slice was 49 ml_{blood} per min and 100ml_{lung} and mean MTT was 4.4 s.

Figure 2. Semi-quantitative MRI parameters of pulmonary parenchymal perfusion

A γ -variate function was fitted to the signal intensity-time curve of the lung parenchyma and semi-quantitative parameters were determined as follows: maximum signal increase (SI) is the difference between maximum and 20% signal intensities of the γ -variate function, upslope is the maximum signal increase per time interval (b), time to peak (TTP) is the time difference between 20% and maximum signal intensities of the curve and full width half maximum (FWHM) is the time difference between 50% signal intensities (c). Note that the curves in b and c represent signal intensity-time curves and not the respective γ -variate function.

Figure 3. Numbers of participants for the different analysis

Depicted are the numbers of included participants (controls and COPD patients) for the different analysis. The number of participants for comparison with global lung perfusion (GLP) was lower, because bodyplethysmography and MRI flow measurements, which are necessary for calculation of GLP, were not available for all participants. Regional lung perfusion was only assessed in controls.

Figure 4. Regression analysis between pulmonary blood flow with the semi-quantitative measures maximum signal increase and upslope

Depicted are the significant positive correlations of pulmonary blood flow (PBF) with maximum signal increase (SI, $r=0.86$, $p<0.001$; A) and PBF with upslope ($r=0.81$, $p<0.001$; B) within the cohort of $n=143$ participants.

Figure 5. Bland-Altman plots of pulmonary blood flow and global lung perfusion

Bland-Altman plots show the difference between pulmonary blood flow (PBF) and global lung perfusion (GLP) against the mean of both values. Data of controls with available measures ($n=26$; A) and COPD participants are plotted ($n=48$; B). The center line displays the mean difference between PBF and GLP. The dashed lines represent the 95% confidence interval. As differences in PBF measured by MRI GLP were not independent of the observed perfusion values, a modified rather than standard Bland-Altman plot was generated as recommended by Bland and Altman for such situation [32]. The plot demonstrates that PBF by MRI under-estimates GLP for very low perfusion values and over-estimates for very high perfusion values. For perfusion values within the normal range PBF measured by MRI and GLP are in excellent agreement.

Figure 6. Regional distribution of pulmonary blood flow in a participant without COPD
 In this participant without COPD, PBF maps are shown of the posterior (a), middle (b) and anterior (c) coronal slice. PBF in the posterior lung is higher (PBF = 112 ml_{blood} per min and 100ml_{lung}; a) than in the anterior lung parenchyma (PBF = 74 ml_{blood} per min and 100ml_{lung}; c) as an effect of gravity in the posterior, dependent portion of the lungs in the supine position.

Table 1

Characteristics of the study population (n=143).

<u>Characteristic</u>	
Age, years	67.7 (7.1)
Gender male, %	59.4
Race/Ethnicity, %	
White	57.3
African-American	21.7
Hispanic	18.2
Other	2.8
Smoking status, %	
Current smoker	32.9
Former smoker	67.1
<u>Pulmonary function</u>	
FVC, %predicted	97.4 (16.1)
FEV ₁ , %predicted	84.6 (23.6)
FEV ₁ /FVC ratio	0.65 (0.14)
DL _{CO} , %predicted (n=87)	59.0 (15.6)
DL _{CO} /VA (n=87)	3.37 (0.85)
Total lung capacity, L (n=87)	5.71 (1.18)
<u>Global pulmonary perfusion</u>	
Blood flow, main pulmonary artery, L/min (n=124)	4.87 (1.01)
Global lung perfusion, ml _{blood} per min and 100ml _{lung} (n=74)	85.8 (20.5)
<u>Quantitative parameters of regional pulmonary parenchymal perfusion</u>	
Pulmonary Blood Flow, ml _{blood} per min and 100ml _{lung}	65.5 (42.5)
Pulmonary Blood Volume, ml _{blood} per 100ml _{lung}	4.33 (2.61)
Mean Transit Time, s	4.42 (1.54)
<u>Semi-quantitative parameters of regional pulmonary parenchymal perfusion</u>	
Signal increase (SI), AU	13.57 (7.72)
Maximum signal increase/time (Slope), AU/s	2.20 (1.47)
Time to peak, s (n=142)	6.86 (1.81)
Full width half maximum, s (n=134)	9.85 (2.95)

Characteristics of the study population of n=143 participants of the MESA COPD study, if not indicated differently. Values are given as mean (standard deviation).

DL_{CO} = diffusion capacity, GLP = global lung perfusion calculated by total lung capacity (TLC), VA = alveolar volume.

Table 2

Coefficients of variation (CV) of quantitative and semi-quantitative parameters of regional pulmonary parenchymal perfusion in the MESA COPD Study

	intraobserver CV (n=20)	interobserver CV (n=20)
<u>Quantitative parameters of pulmonary parenchymal perfusion</u>		
Pulmonary blood flow	6.8%	7.6%
Pulmonary blood volume	6.8%	7.0%
Mean transit time	1.5%	3.1%
<u>Semi-quantitative parameters of pulmonary parenchymal perfusion</u>		
Maximum signal increase	2.0%	7.9%
Maximum signal increase/time interval (Upslope)	2.8%	7.5%
Time to peak	1.7%	2.8%
Full width half maximum	1.3%	3.6%

Table 3

Correlation between quantitative and semi-quantitative parameters of regional pulmonary parenchymal perfusion in the MESA COPD Study

	Signal increase	Upslope	Time to Peak	Full width half maximum
Pulmonary Blood Flow	0.86 <0.001	0.81 <0.001	-0.36 <0.001	-0.26 0.003
Pulmonary Blood Volume	0.74 <0.001	0.67 <0.001	-0.23 0.045	-0.08 0.36
Mean Transit Time	-0.50 <0.001	-0.47 <0.001	0.56 <0.001	0.57 <0.001

P-values are indicated below each correlation coefficient.

Table 4

Correlation coefficients between parameters of quantitative and semi-quantitative regional pulmonary parenchymal perfusion with global lung perfusion and diffusing capacity

n=74	Global lung perfusion	%predicted DL_{CO}	DL_{CO}/VA
Pulmonary blood flow	0.42	0.25	0.36
	<0.001	0.029	0.002
Pulmonary blood volume	0.32	0.21	0.30
	0.005	0.07	0.01
Mean transit time	-0.39	-0.28	-0.34
	<0.001	0.016	0.003
Signal increase	0.47	0.34	0.47
	<0.001	0.003	<0.001
Upslope	0.43	0.28	0.43
	<0.001	0.017	<0.001
Time to peak (n=73)	-0.13	-0.14	-0.17
	0.27	0.25	0.15
Full width half maximum (n=70)	-0.35	-0.17	-0.27
	0.003	0.16	0.023

Correlations for n=74 participants with available measures. P-values are indicated below each correlation coefficient.

Table 5
Regional distribution of pulmonary parenchymal perfusion in participants without COPD

n=63	right lung	left lung	p-value	posterior lung	anterior lung	p-value	superior lung	inferior lung	p-value
Quantitative parameters of pulmonary parenchymal perfusion									
Pulmonary blood flow, ml _{blood} per min and 100ml _{lung}	87.52 (50.69)	81.12 (44.11)	0.032	137.19 (63.51)	83.66 (42.80)	<0.001	91.22 (54.46)	75.96 (44.09)	<0.001
Pulmonary blood volume, ml _{blood} per 100ml _{lung}	5.75 (2.72)	6.19 (3.13)	0.004	7.77 (3.76)	5.14 (2.54)	<0.001	5.46 (3.29)	4.92 (2.98)	0.014
Mean transit time, s	3.70 (1.04)	3.89 (1.19)	<0.001	3.50 (1.12)	3.93 (1.22)	<0.001	3.93 (1.50)	4.06 (1.16)	0.18
Semi-quantitative parameters of pulmonary tissue perfusion									
Signal increase, AU	23.20 (10.35)	24.59 (7.33)	0.012	34.86 (16.38)	19.76 (9.98)	<0.001	14.66 (7.41)	19.18 (8.31)	<0.001
Upslope, AU/s	4.03 (2.11)	4.36 (2.29)	0.005	6.41 (3.39)	3.34 (2.02)	<0.001	2.72 (1.68)	3.01 (1.62)	0.09
Time to peak, s	6.35 (1.44)	6.27 (1.30)	0.36	5.74 (1.04)	6.59 (1.70)	<0.001	6.23 (1.89)	7.02 (1.94)	0.004
Full width half maximum, s	9.34 (2.29)	9.64 (2.93)	0.09	9.20 (2.15)	9.51 (2.98)	0.16	9.65 (4.45)	9.81 (2.64)	0.10

Regional distribution of perfusion in participants without COPD (n=63 participants). Perfusion values for the right and left lung display mean values of the central coronal slice. For quantification of perfusion differences in gravitational direction mean perfusion values of the posterior and the anterior slice (averaged over both lungs) were compared. For assessment of perfusion differences in isogravitational direction the lung was divided into three thirds on the central coronal slice. Values for the superior lung display mean values over the superior thirds of both lungs; values for the inferior lung display mean values over the inferior thirds of both lungs.