Acute COPD exacerbation: 3 T MRI evaluation of pulmonary regional perfusion — Preliminary experience☆

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Summary
Objectives: To compare pulmonary perfusion parameters by means of dynamic perfusion magnetic resonance in patients affected by chronic obstructive pulmonary disease (COPD), during and after acute exacerbation.
Methods: Fifteen patients were successfully evaluated with perfusional MRI during an acute exacerbation of COPD and upon clinical stabilization. Inclusion criteria were a PaCO2 > 45 mmHg and respiratory acidosis (arterial blood pH < 7.35) at admittance.
Results: In the acute phase a reduction of pulmonary blood flow (PBF) and pulmonary blood volume (PBV), and a significant prolonging of the mean transit time (MTT) and time to peak (TTP) were observed in all patients. In the stabilization phase a significant increase of PBF and PBV and a significant reduction of MTT and TTP were observed in 6 patients; no significant variations were observed in the other 9 patients.
Conclusion: 3D time-resolved contrast-enhanced MRI allows quantitative evaluation of pulmonary regional perfusion in patients affected by COPD, identifying patients in which perfusion defects are resolved in the clinical-stabilization phase.

☆ All the authors contributed equally to this paper and state: that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors.
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Introduction

The evaluation of pulmonary perfusion plays a major role in the study of lung function and in the understanding of pulmonary pathophysiology. Changes in regional parenchymal perfusion can be encountered in some lung diseases such as pulmonary embolism, chronic obstructive pulmonary disease (COPD), pulmonary hypertension and lung cancer [1–5]. Evaluation of regional lung perfusion may be used in the differential diagnosis between different diseases by demonstration of a characteristic perfusion pattern. Moreover, the evaluation of a specific pulmonary perfusion pattern may be used to improve the therapy planning [6].

Several techniques have been used for the assessment of pulmonary perfusion including lung perfusion scintigraphy [7] and dynamic computed tomography [8]. Radionuclide techniques based on intravenous administration of radioactive macro-aggregates have been widely used for many years and currently scintigraphy and SPECT represent the gold standard [9]. These techniques, however, expose the patient to ionizing radiations and have a reduced spatial and temporal resolution, which results in a reduced anatomical definition and low functional sensitivity [10,11].

Early effective studies on pulmonary perfusional MR were performed using angiographic sequences with paramagnetic contrast [12–15]. The currently used techniques are based on 2D and 3D Fast Field-Echo (FFE) dynamic sequences, and on Echo Planar Imaging (EPI) [5]. On this basis, the aim of our study was to compare the pulmonary perfusion parameters in patients during and after an acute COPD exacerbation with hypercapnic syndrome, using dynamic perfusion magnetic resonance.

Materials and methods

Patients

Fifteen patients affected by COPD were evaluated by perfusional MRI between October 2011 and July 2012 (12 men and 3 women; age range: 65–78 yrs; mean age: 71.4 ± 4.5 yrs). All participants had a diagnosis of moderate to severe COPD according to the Global Initiative for Obstructive Lung Disease classification [16] and had been admitted to the emergency department under acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and then referred to the pulmonary disease department [17–19]. Overall clinical and laboratory examinations were evaluated by a pulmonologist. Inclusion criteria were an arterial carbon dioxide tension (PaCO₂) greater than 45 mmHg and respiratory acidosis with arterial blood pH of <7.35 [20,21]. All patients presented with clinical signs suggestive of right heart failure. We excluded patients with diagnosis of interstitial lung diseases primary and secondary to collagen pathologies, exposure to drugs or environmental toxics agents, cardiac diseases and history of chest radiation therapy.

Functional MR was performed, for each patient, after hospital admission during the acute respiratory distress phase, and upon clinical stabilization before discharge.

Our Institutional Review Board approved the experimental protocol and all patients were given an explanation of the purpose of the study and provided written informed consent.

Perfusional MR imaging technique

MR imaging was performed with a 3.0 T MR scanner (Achieva 3 T; Philips Healthcare, Best – The Netherlands). A six-element phased-array coil was used. A 20-gauge cannula was positioned in the right antecubital vein and connected to an electronic power injector (MR Spectris; Medrad, Pittsburgh, PA).

After scout images were obtained, an inspiratory breath-hold dynamic 3D time-resolved T1-weighted turbo field-echo sequence was performed (repetition time 2.6 ms/echo time 1.3 ms; flip angle: 10°; turbo factor: 40; sensitivity-encoding factor: 3; field of view of 435 × 326 mm; reconstruction matrix 256 × 256; spatial resolution: 1.7 x 1.3 mm). All acquisitions were performed on axial plane including both lungs. We covered a slab of 300 mm divided in 30 over-contiguous partitions leading to a section thickness of 5 mm. The first volume was acquired during breath-hold before starting the contrast medium injection and was used as reference for subtraction.

Eight milliliters (0.5 mmol/mL) of gadopentetate dimeglumine (Magnevist; Bayer HealthCare, Wayne, NJ) was injected at 4 mL/s, followed by 20 mL of saline solution administered with the same flow rate. Image acquisition was obtained without any delay since the beginning of the injection of the contrast medium (delay time: Ø s).

The scan time for each 3D dataset was 1.5 s. Ten consecutive sequences were performed in an overall time of 15 s of inspiratory breath-hold. Patients were asked to hold their breath as long as possible during the data acquisition. Cardiac triggering or respiratory gating was not used.

Data analysis

The color-coded perfusion maps were generated with a workstation (ViewForum; Philips Healthcare, Best – The Netherlands) and a radiologist and a pulmonologist in consensus processed the acquisition data with the purpose of calculating the signal intensity versus time (SI/t) curves, obtained by the placement of Regions of Interest (ROIs). Two lung-shaped ROIs were drawn defining the full extent of both lungs, excluding the hilar vascular structures. A
single ROI was also drawn in correspondence of the trunk of the pulmonary artery as reference of pulmonary arterial flow (Figs. 1 and 2). Subsequently, 6 ROIs (3 for each lung) were plotted on different peripheral areas of the lung, avoiding large vessels, for the evaluation of the regional perfusion (Fig. 3). All the ROIs were placed with free hand drawing, taking care to avoid areas whose signal was clearly determined by motion artifacts. The data obtained by the 6 parenchymal ROIs were used, together with the lung-shaped ones, to produce average perfusion data, less dependent from physiological i.e., gravity blood stasis, and pathological causes i.e., parenchymal consolidations, scar tissues, bronchiectasis or emphysema bullae.

Initially, perfusion values obtained from the lung-shaped ROIs were averaged with the median values calculated from the 3 regional ROIs. Subsequently, these values were averaged with the ones calculated from the contralateral lung and normalized using the ROI put in the pulmonary trunk.

The SI/t curves generated by measuring the signal intensity in ROIs drawn in each patient before and after medical therapy were analyzed in order to calculate the perfusion data. The values of the SI/t curves calculated in correspondence of the peripheral lung ROIs were normalized to the values of the SI/t curves of the ROI drawn at the trunk of the pulmonary artery, in order to avoid artifacts due to the different impedances of pulmonary blood flow.

In order to extract quantitative indices such as Pulmonary Blood Flow (PBF; mL/100 mL of lung tissue/min), Pulmonary Blood Volume (PBV; mL/100 mL of lung tissue), Mean Transit Time (MTT; s) and Time To Peak (TTP; s), SI/t curves were fitted to a gamma variate function using an algorithm described in previous studies, such as the ones by Hatabu–Tadamura; Uematsu–Levin; Jang–Oh [11,22,23].

Patients in which a normalization of at least two perfusion parameters was observed in the clinical-stabilization phase MR composed Group 1; patients in which a normalization of less than two perfusion parameters resulted normalized in the clinical-stabilization phase MR composed Group 2. Normalization of a perfusion parameter was defined as a value comprised in the range of the control group described in a previous reports [24,25].

**Statistical analysis**

The comparison of each perfusion parameter between the two observations for each group of patients was performed using a paired Student “t” test; descriptive graphs, P value and $R^2$ ($r$) were obtained using GraphPad Prism 5.0 (GraphPad Software, Inc. La Jolla, CA, USA).

**Results**

Dynamic pulmonary MR angiography was successfully acquired in all enrolled subjects. The functional MRI evaluation of pulmonary perfusion performed during acute clinical phase demonstrated in all patients a reduction of PBF (Mean: 63.47 ± 8.983 mL/100 mL/min; 95% C.I. 58.49–68.44) and PBV (4.653 ± 0.9125 mL/100 mL; 95% C.I. 4.148–5.159), and a significant prolonging of MTT (Mean: 7.593 ± 1.706 s; 95% C.I. 6.649–8.538) and TTP (Mean: 4.740 ± 1.093 s; 95% C.I. 4.135–5.345), compared with the normal physiologic values [14,24,25]. The evaluation of pulmonary perfusion acquired performed during the clinical stabilization compared to those acquired in the acute phase.
showed an overall significant reduction of MTT (Mean: 6.087 ± 1.828 mL/100 mL; 95% C.I. 5.074–7.099, difference $P = 0.0382$) and TTP (Mean: 3.747 ± 1.056 s; 95% C.I. 3.162–4.331, difference $P < 0.0142$); no significant differences were observed among the mean PBF (91.8 ± 38.93 mL/100 mL/min 95% C.I. 70.24–113.4, $P = 0.0638$) and PBV (Mean: 7.367 ± 4.577 mL/100 mL 95% C.I. 4.832–9.901, difference $P = 0.05$) values.

In 6 patients the functional MRI evaluation of pulmonary perfusion performed during clinical-stabilization phase showed a normalization of all the perfusion parameters, with a significant increase of PBF (136.3 ± 14.4 mL/100 mL/min; 95% CI: 121.2, 151.5; $R^2 = 0.97; P_{value} < 0.0001$) and PBV (11.8 ± 4.2 mL/100 mL; 95% CI: 7.4, 16.3; $R^2 = 0.8; P_{value} = 0.0059$) and a significant reduction of MTT (4.6 ± 1 s; 95% CI: 3.6, 5.7; $R^2 = 0.96; P_{value} < 0.0001$) and TTP (2.8 ± 0.7 s; 95% CI: 2, 3.5; $R^2 = 0.84; P_{value} = 0.0034$); these patients were defined as Group 1 (Fig. 4). The remaining 9 patients showed no significant changes in PBF (62.1 ± 6.5 mL/100 mL/min; 95% C.I.: 57.1, 67.1; $R^2 = 0.06; P_{value} < 0.4858$), PBV (4.39 ± 0.7 mL/100 mL; $R^2 = 0.0005; 95\% C.I.: 3.8, 4.9; P_{value} < 0.9493$) and no significant reduction of MTT (7 ± 1.65 s; $R^2 = 9.283e-005; 95\% C.I.: 5.7, 8.3; P_{value} = 0.9789$) and TTP (4.39 ± 0.7 s; $R^2 = 9.283e-005; 95\% C.I.: 5.7, 8.3; P_{value} = 0.9789$) in the acute COPD exacerbation in 6 patients (group 1).

Figure 3 Coronal quantitative color-coded perfusion maps in a 62-year-old woman with acute COPD exacerbation. 6 ROIs (3 for each lung) were plotted on different peripheral areas of both lungs (L1–L3: right lung; L4–L6: left lung), avoiding large vessels, for the evaluation of the regional peripheral perfusion.

Figure 4 The graphic shows modification of functional parameters such as PBF, PBV, MTT and TTP obtained during and after the acute COPD exacerbation in 6 patients (group 1).
Discussion

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, with an increasing prevalence during the past decades. One established complication of COPD is the development of pulmonary hypertension (PH), which leads to right ventricular enlargement and hypertrophy [26]. When the adaptive mechanisms of right ventricular dilatation and hypertrophy cannot compensate for the hemodynamic burden, right heart failure, with poor prognosis, occurs [27]. Typically, PH appears when airflow limitation is severe and is associated with chronic hypoxemia.

The normal gas exchange in the lung is provided by the perfect balance between ventilated and perfused areas which is pathologically altered in COPD. The consequent hypoxic vasoconstriction of pulmonary vessels, that represent the main mechanism to attempt to maintain a correct V/Q ratio, leads to a reduction of perfusion in non-ventilated lung areas. A second adjustment mechanism of V/Q ratio is the pulmonary hypercapnic vasoconstriction, opposite to the systemic hypercapnic vasodilation [28,29]. Furthermore some abnormalities, including pulmonary vascular remodeling, reduction of pulmonary vessels and pulmonary thrombosis, which influence pulmonary arterial pressure determining the increase in pulmonary vascular resistance index (PVRI) and the onset of pulmonary hypertension and right heart failure, are commonly found in COPD [26].

The increased PVRI is the result of the combination or irreversible and potentially reversible mechanisms. Arterial obstruction, obliteration and remodeling are accountable for the irreversible component, while active increases in vascular tone for the reversible one, which, in some cases, may represent more than 50% of PVRI and can be potentially susceptible to pharmacological treatment [26,27].

3D time-resolved MR angiography allows the evaluation of pulmonary hemodynamic parameters, such as PBF, PBV, MTT and TTP, which significantly correlate with the same parameters obtained through invasive techniques [30].
In this study, we measured the regional pulmonary arterial quantitative indices using 3D time-resolved MR angiography in patients affected by COPD, during the acute hypercapnic syndrome phase and upon the clinical-stabilization phase. In all patients a significant reduction of PBF and PBV during the acute hypercapnic syndrome was documented, suggesting the presence of pulmonary hypoperfusion with a characteristic peripheral mantel distribution pattern. In these patients, moreover, MTT and TTP were significantly prolonged, compared to the normal physiologic values reported in the literature [24,25].

Previous studies [11,25] described a reduced MTT in patients affected by COPD, which appear to be in contrast with our finding of an increased MTT. We believe that this discrepancy may be a result of the fact that the patients evaluated in this study were experiencing an acute COPD exacerbation with hypercapnic syndrome, which may have determined a significant increase of the pulmonary arterial pressure. Consistently with that, pulmonary hypertension has been shown to be associated with a prolonged MTT [24].

Two groups of patients, which presented different normalization of SI/t-derived values in the functional MRI executed during the clinical-stabilization phase, were identified. In group 1 a significant increase of PBF and PBV with a normalization trend of MTT and TTP values was observed, suggesting in these patients the prevalence of reversible mechanisms accountable for hypoperfusion i.e., peripheral hypoxic/hypercapnic vasoconstriction. In group 2, no substantial variation of PBF, PBV, MTT and TTP values between the acute phase and the clinical-stabilization phase was observed. This observation suggest the presence of underlying irreversible mechanisms in patients belonging to this group, possibly due to extensive vascular remodeling or thromboembolic events.

Previous studies demonstrate the feasibility at 3.0 T of 3D contrast-enhanced MR angiography, which allows a detailed morphological evaluation of the pulmonary vasculature and provides hemodynamic functional information [30,31]. Higher SNR at 3.0 T is an important element for increasing spatial resolution and is likely to improve visualization of small blood vessel segments [32,33].

In patients presenting severe pulmonary function impairment, poor breath-hold capability may result in underestimation or overestimation of regional perfusion and regional pulmonary function due to motion artifacts [24]. Our results demonstrate the feasibility of using 3D time-resolved contrast-enhanced MRI to quantitatively evaluate pulmonary regional perfusion in patients affected by COPD.

Lung parenchyma has a very short T2 value ranging from 0.9 to 2.2 ms, due to the multiple interface of air and soft tissue produced by the alveoli, which cause large local magnetic field gradients and dephase the MR signal [9,30,34]; thus we attempted to obtain a better MR signal from the lung parenchyma by using a 3.0 T field, which provides a higher SNR compared with lower fields such as 1.5 T, and performed a transaxial 3D T1-weighted turbo field-echo sequence, which need a short echo time (1.3 ms). The angiographic technique described in this study yields time-resolved images of the pulmonary circulation, from which physiologic information can be calculated. To reduce acquisition times and improve temporal and spatial resolution, we used the sensitivity-encoding technique [35], which improves the compliance of patients with decreased respiratory reserve, unable to perform prolonged and repeated apnea, by reducing the overall scan time. Indeed the poor breath-hold capability determines an increase of the MR signal, which reduces the magnetic susceptibility effects [12,13]. As described in previous reports, we administered a low dose (8 mL) of contrast agent. A high dose (20 or 40 mL) of contrast agent has been shown to produce the most intense parenchymal enhancement, while a low dose (5 mL) has been shown to provide a better recirculation imaging [12,13]. As to avoid artifacts in the perfusion parameters calculation, an adequate molality (0.5 mmol/mL) and an intermediate

<table>
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<th>Table 1</th>
<th>Values of PBF, PBV, MTT and TTP of Group 1 and Group 2 patients, evaluated with dynamic pulmonary MR angiography during the acute respiratory distress phase and during the clinical-stabilization phase.</th>
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<td>Group 1a</td>
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<td></td>
<td>Acute phase</td>
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<td>Clinical stabilization</td>
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<td>PBF (mL/100 mL of lung tissue/min)</td>
<td>64.3 ± 12.3</td>
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<td></td>
<td>95% C.I.: 51.4–77.3</td>
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<tr>
<td>PBV (mL/100 mL of lung tissue)</td>
<td>5 ± 1</td>
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<td>95% C.I.: 3.9–6.1</td>
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<tr>
<td>MTT (s)</td>
<td>8.4 ± 1.5</td>
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<td>95% C.I.: 6.8–10</td>
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<td>TTP (s)</td>
<td>4.9 ± 1.1</td>
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<td>95% C.I.: 3.8–6.1</td>
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PBF = pulmonary blood flow; PBV = pulmonary blood volume; MTT = mean transit time; TTP = time to peak.

a Group 1 identifies the 6 patients in which an improvement of the perfusion parameters was observed in the clinical-stabilization phase.

b Group 2 identifies the 9 patients in which no significant changes in the perfusion parameters were observed between the acute and the stabilization phase.
dosage (8 mL) of contrast media were chosen. As mentioned in previous reports [36], these molality and volume combination determine an average contrast media dose of 0.057 mmol/kg of body weight, which is sufficient to avoid artifacts in the calculation of the perfusion parameters determined by the linear correlation between contrast media concentration and signal intensity determined by low contrast doses.

Our study is characterized by some limitations. In first place, the number of patients included was small, which makes a further evaluation of a larger cohort of patients required for more accurate conclusions. A second limitation is the quite long inspiratory breath-hold used in this study which, although all enrolled patients were able to complete the MRI evaluation, may not be feasible in all patients with impaired respiratory compliance in a real life clinical setting. Finally, the evaluation of pulmonary perfusion by MR may be influenced by volume variations such as those occurring in inspiratory and expiratory breath-hold. Pulmonary perfusion during breath-hold depends on the inspiratory level, in fact higher perfusion is commonly observed at expiratory breath-hold, thus making a strict breath-hold standardization protocol and patients compliance mandatory for the good accuracy of this diagnostic technique [37].

In conclusion, 3D time-resolved contrast-enhanced MRI is useful for a quantitative evaluation of regional perfusion in patients affected by COPD. The comparative evaluation of perfusion parameters obtained during an acute COPD exacerbation and upon clinical stabilization, may be useful in the identification of patients in whom the hypoperfusion due to vasospasm is the main responsible of pulmonary hypoperfusion during acute COPD exacerbation with potential advantages on the clinical management of these patients.

Conflict of Interest Statement

We declare that we have no conflict of interest with this study that has not been sponsored by any Private Company.

References


