Acute COPD exacerbation: 3 Tesla MRI evaluation of pulmonary regional perfusion - preliminary experience.

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Purpose

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 neoplasms [1-5]. Evaluation of regional lung perfusion may be used in the differential diagnosis between different diseases by demonstration of a characteristic perfusion pattern, also improving the therapeutic 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 using 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 both 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.
Methods and Materials

Patients

Twenty-nine patients affected by COPD, at risk of cardiac-respiratory failure, were evaluated by perfusional MRI Between October 2011 and November 2012 (23 men and 6 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 pulmonary disease department under acute exacerbation of chronic obstructive pulmonary disease (AECOPD) [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]. 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 during 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 Tesla MR scanner (Achieva 3.0T; 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 msec/echo time 1.3 msec; flip angle: 10°; turbo factor: 40; sensitivity encoding factor: 3; field of view of 435 x 326 mm; reconstruction matrix 256 x 256). 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.

Six-eight milliliters of gadopentetate dimeglumine (Magnevist; Bayer HealthCare, Wayne, NJ) was injected at 4 mL/sec, 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 sec).
The scan time for each 3D dataset was 1.5 seconds. Ten consecutive sequences were performed in 15 seconds asking patients to hold their breath as long as possible during the acquisition. Cardiac triggering or respiratory gating were used.

Data Analysis

The color-coded perfusion maps were generated with a workstation (ViewForum; Philips Healthcare, Best - The Netherlands) and two radiologists in consensus processed the acquisition data. Two Regions of Interest (ROIs) were drawn defining the full extent of both lungs, excluding the hilar vascular structures; and a third single ROI was also drawn in correspondence of the trunk of the pulmonary artery as reference of pulmonary arterial flow (Figure 1, 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 (Figure 3).

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. [22-24].

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 [25, 26].

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 square (r) were obtained using GraphPad Prism 5.0 (GraphPad Software, Inc. La Jolla, CA, USA).
Fig. 1: Figure 1. Contrast-enhanced perfusion MRI (TR/TE, 2.6/1.3) with a temporal resolution of 1.5 s after application of gadopentetate dimeglumine in a 63-year-old man with acute COPD exacerbation. Coronal maximum intensity projection (MIP) image showing enhancement of lung arterial vessels. Two ROIs (L1 and L2) were drawn in order to calculate SI/t curves, defining the full extent of both lungs, excluding the hilar vascular structures. A third ROI (L3) was drawn at the trunk of the pulmonary artery in order to normalize the values of SI/t curves of the peripheral and avoiding artifacts due to the different impedances of pulmonary blood flow.

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Fig. 2: Figure 2. Coronal quantitative color-coded perfusion maps in a 69-year-old man with acute COPD exacerbation showing the correct tracking of ROIs on both lungs, with exclusion of hilar vascular structures. It’s important to note the presence of areas with reduced/absent flow suggestive for pulmonary hypoperfusion, with a pattern of peripheral mantel distribution.

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**Fig. 3:** 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 to L3: right lung; L4 to L6: left lung), avoiding large vessels, for the evaluation of the regional peripheral perfusion.

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**Fig. 4:** 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).

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Fig. 5: Figure 5. The graphic shows modification of functional parameters such as PBF, PBV, MTT and TTP obtained during and after the acute COPD exacerbation in 9 patients (group 2).

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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 (63.5±8.9; 95% confidence interval [CI]: 58.5, 68.4) and PBV (4.6±0.9; 95% [CI]: 4.1, 5.1), and a significant prolonging of MTT (7.6±1.7; 95% [CI]: 6.6, 8.5) and TTP (4.7±1.1; 95% [CI]: 4.1, 5.3) (Figure 4, 5), compared with the normal physiologic values [14, 25, 26].

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; r = 0.97; 95% CI: 121.2, 151.5; P_value < 0.0001) and PBV (11.8±4.2; r = 0.8; 95% CI: 7.4, 16.3; P_value = 0.0059) and a significant reduction of MTT (4.6±1; r = 0.96; 95% CI: 3.6, 5.7; P_value < 0.0001) and TTP (2.8±0.7; r = 0.84; 95% CI: 2, 3.5; P_value = 0.0034) in 18 patients; these patients composed Group 1 (Figure 4). The remaining 11 patients showed no significant changes in PBF (62.1±6.5; r = 0.06; 95% CI: 57.1, 67.1; P_value < 0.4858), PBV (4.39±0.7; r = 0.0005; 95% CI: 3.8, 4.9; P_value < 0.9493) and no significant reduction of MTT (7±1.65; r = 9.283e-005; 95% CI: 5.7, 8.3; P_value = 0.9789) and TTP (4.39±0.7; r = 0.1029; 95% CI: 3.8, 4.9; P_value = 0.3663) were observed; these patients composed group 2 (Figure 5).

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 [27]. When the adaptive mechanisms of right ventricular dilatation and hypertrophy cannot compensate for the hemodynamic burden, right heart failure, with poor prognosis, occurs [28]. Typically, PH appears when airflow limitation is severe and is associated with chronic hypoxemia.

The normal gas exchange in the lung provides a perfect balance between ventilated and perfused areas, the so-called ventilation-perfusion (V/Q) ratio, which is pathologically altered in COPD. The hypoxic vasoconstriction of the pulmonary vessels, the main mechanism for maintaining a correct V/Q ratio, leads to a reduction in non-ventilated lung perfusion. A second adjustment mechanism of V/Q ratio is the pulmonary hypercapnic vasoconstriction, opposite to the systemic hypercapnic vasodilation [29, 30]. Furthermore some abnormalities, including pulmonary vascular remodelling, reduction of pulmonary vessels and pulmonary thrombosis, which influence pulmonary perfusion determining the increase in pulmonary vascular resistance index (PVRI) and the onset of pulmonary hypertension and right heart failure, are commonly found in COPD [27].

The PVRI increase may be fixed and/or potentially reversible. Arterial obstruction, obliteration and remodelling are responsible for the fixed component, while active
increases in vascular tone are responsible for the reversible component, which may account for >50% PVRI and can be treated pharmacologically. [27, 28].

Dynamic perfusion MR angiography with 3D time-resolved sequences allows the evaluation of pulmonary hemodynamic parameters, such as PBF, PBV, MTT e TTP, which significantly correlate with the same parameters obtained through invasive techniques [31].

In this study, we measured the regional pulmonary arterial quantitative indices in patients affected by COPD, during the acute hypercapnic syndrome phase and during the clinical stabilization phase. In all patients a significant reduction of PBF and PBV during the acute hypercapnic syndrome was shown, suggestive for pulmonary hypoperfusion with a characteristic pattern of peripheral mantel distribution. In these patients, moreover, MTT and TTP were significantly prolonged, compared to the normal physiologic values [25, 26].

Functional MRI evaluation executed during the clinical stabilization phase identified two groups of patients, which presented different normalization of SI/t-derived values. In group 1 a significant increase of PBF and PBV with a normalization trend of MTT and TTP values was observed; in these patients can be assumed a predominant role of the pulmonary hypoxic vasoconstriction as responsible of parenchimal hypoperfusion during the acute exacerbation phase, which resolves during clinical stabilization phase with the cessation of vasoconstrictive hypoxic stimulus. In group 2, no substantial variation of PBF, PBV, MTT and TTP values between the acute-phase and the clinical-stabilization phase MR was observed; in our opinion, these data suggest a state of irreversible hypoperfusion, that can't be resolved with the recovery of a normal pulmonary ventilation during clinical stabilization phase, supported by mechanisms mentioned above, as for example thromboembolic hypoperfusion [27].

Previous studies demonstrate the feasibility at 3.0 T of dynamic 3D contrast-enhanced MR angiography, which allows a detailed morphological evaluation of the pulmonary vasculature and provides hemodynamic functional information [31, 32]. 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 [33, 34].

Lung parenchima 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, 31, 35]; thus we performed an axial 3D T1-weighted turbo field-echo sequence with a short echo time. 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 [36], which improves the compliance of patients with decreased respiratory reserve, unable to perform prolonged and repeated apnea.
A reduced administration of medium contrast is a further advance of the acquisition technique used in this study. In fact, when using ultra-short echo-time sequences, the administration of gadolinium-based contrast agent 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 (6 to 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].

Our study is characterized by some limitations. First, the number of patients included was small, which makes necessary a further evaluation in a larger cohort of patients for more accurate conclusions.

A second limitation is the fifteen-second inspiratory breath-hold used in this study, which may not be feasible in all patients with impaired respiratory compliance. 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 [25]. Our results demonstrate the usefulness dynamic high temporal resolution sequences to quantitatively evaluate pulmonary regional perfusion in patients with reduces breath-hold capability as in COPD.

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].
Conclusion

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


