Non-invasive assessment of pulmonary arterial hypertension with 3D Time-resolved MR angiography in patients with idiopathic pulmonary fibrosis

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Purpose

Idiopathic Pulmonary Fibrosis (IPF) is a chronic progressive disease, with unknown etiology, characterized by a severe fibrotic degeneration of pulmonary parenchyma. The most common symptoms are under-stress dyspnea and chronic dry cough[1]. This disease is classified in a lung disease family known as parenchymal interstitial diseases within the subgroup of idiopathic interstitial pneumonia.

A research carried out on a large group of people in the U.S.A. revealed a prevalence in population of 42.7 cases/100.000 and an incidence of 16.3 cases/100.000/year, according to wide inclusion criteria, whereas they were respectively of 14 cases/100.000 and of 6.8 cases/100.000/year on the basis of restricted inclusion standards[2]. A later research carried out in the United kingdom reported an incidence of 4.6 cases/100000 in habitants/year[3].

By definition, the cause of IPF is unknown. The term 'idiopathic' means that there are not known causes responsible for the onset of the disease, even if a certain habits and environmental etiology for IPF is supported by several sources[4,5,6]. For this reason IPF diagnostic criteria require the exclusion of known causes of pulmonary fibrous disease.

The natural history of IPF is not well defined. It has recently acknowledged that the clinical course is highly variable, with many patients remaining stable for a prolonged period of time, even in the absence of effective medical treatment, while others experience a rapid and aggressive progression. In addition, in some cases, the clinical course consists rather than on a gradual decline, on a step-like process, with periods of stability alternating with acute respiratory worsening[7]. Some of these events meet the criteria of acute exacerbations (AEs) and carry a high mortality.

Likely pulmonary fibrosis is the result of a variety of attacks occurred at lung level including toxic, auto-immune, pharmacologic, infectious or traumatic lesions. The type of the lung parenchyma response probably depends on various factors of the host such as age, genetic predisposition and environment elements. The pathologic alterations resulting in the pulmonary tissue may be heterogeneous but with distinctive overlaps characterized by different degrees of inflammation and fibrosis[8]. Several authors suggest that the attack to the alveolar epithelium is followed by a fall of pro-inflammatory and fibro-proliferative mediators that produce responses associated with normal tissue repair. For same not clear reasons, such processes may not occur causing progressive fibrosis through a process of parenchymal remodeling[9-11]. Moreover some anatomic and clinical researches have also suggested a role of endothelial vascular factors of growth, whose activation might have a role in the development of fibrosis and remodeling of the pulmonary arterial circulation, responsible for Pulmonary Arterial Hypertension (PAH) in patients with IPF[12]. PAH is a physio-pathologic condition characterized by vascular growth and proliferation producing an increase of vascular resistance and right heart failure. PAH is usually distinguished into an idiopathic (IPAH) and a secondary
form associated to other morbid conditions or exposures to etiological factors[13]. The classification of WHO distinguishes Pulmonary Hypertension (PH) into five groups on the basis of pathogenic mechanisms rather than on the ground of associated pulmonary diseases. PAH is defined as an increase of pulmonary arterial pressure, that is higher than 25 mmHg at rest or higher than 30 mmHg during a physical exercise, with pulmonary capillary wedge pressure (PCWP) and tele-diastolic pressure in the right ventricle lower than 15 mmHg[1]. According to Nadrous et al. a significant increase of PAH is not limited to patients with advanced form of IPF and is probably higher than is generally supposed.

Also, PAH has important prognostic and therapeutic implications in patients suffering from IPF[14].

Echocardiography with Duple ultrasound evaluation is generally used to evaluate arterial systolic pulmonary pressure. However echocardiography may be inaccurate causing a considerable overvaluation of PAH, preventing to measure in a direct way vascular pulmonary resistances (RVP)[15]. Right heart catheterization (RHC) allows to measure in an accurate way pulmonary hemodynamic parameters, such as pulmonary vascular resistances (PVR) and mean pulmonary arterial pressure (mPAP)[1,15]. The diagnostic utility of the measurement of the caliber of the principal pulmonary arteries at 3 cm from the bifurcation by CT, that proved to have a 84% sensitivity and a 75% specificity, even in absence of a direct connection with arterial pulmonary pressure, was not proved in later researches[16,17]. It was proved as MR angiography (MRA), at high temporal resolution, it is a non-invasive technique that allows to carry out an anatomic and hemodynamic valuation of the pulmonary circle. The analysis of signal intensity versus enhancement time curves of pulmonary vessels, allowed to obtain two parameters of physiological meaning, as time to peak (TTP) and mean transit time (MTT)[18].

Based on our experience, the aim of our study was to evaluate the effectiveness of high-temporal-resolution MR angiography (HTR-MRA) as a complementary diagnostic tool in the management of patients affected by PAH secondary to IPF.
Methods and Materials

Patients. 35 patients with IPF (21 male and 14 female, average age 64±8.2 years, range 55 - 76 years) were included in the study. The inclusion criteria were: presence of an extensive pulmonary parenchymal disease with significant fibrosis evidenced by pulmonary CT scan. These are defined as reticular opacities, with honeycomb aspect, architectural distortion and/or traction bronchiectases; ground glass focal opacities and/or ground glass condensation areas at any rate associated but not too much prominent. Exclusion criteria were diagnosis of collagen pathologies, cardiac pathologies, included myocardium infarct, or hematological pathologies. All patients underwent right heart catheterization and HTR-MRA. RHC was performed within 10 days from HTR-MRA.

At the moment of the MR angiography no patient had temperature, infection evidence, inflammation pathologies or any form of malignant disease. Thirty-five healthy normotensive volunteers were used as control group. All subjects had a negative case history for cigarette smoking, interstitial lung pathologies as drug toxicity, exposure to drugs or environmental toxins, collagen pathologies, cardiac pathologies or radiation therapy. All controls did not present signs of pulmonary arterial hypertension at an echocardiographic examination.

The research was approved by the inner Ethic Committee. All patients and (control) healthy subjects subscribed an informed consent.

Right Heart Catheterization (RHC). Pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP) were measured by a 7 French (Swan-Arrow or Swan-Abbott) double light balloon-tipped catheter set in the pulmonary artery. The systolic output and the cardiac output (CO) were measured by thermo-dilution. Mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistances (PVR) were determined using the following formula:

\[ mPAP \text{ (in mmHg)} = \text{diastolic PAP} + \left(\text{systolic PAP} - \text{diastolic}\right) / 3; \]

\[ PVR \text{ (in mmHg/L/min)} = (mPAP - \text{mean CIP}) / \text{CO}. \]

For an exact comparison, the mPAP of the different subjects was compared without taking into account the differences of their body dimensions, as this value is independent from the system dimensions, while the PVR were expressed as:

\[ PVR\text{Index(PVRI)}(\text{in mmHg/L/min/m}^2) = \text{PVR/area of bodysurface}, \]

as the PVR are proportional to the system dimensions.
**MRI Imaging.** HTR-MRA was performed by a MR 3.0 Tesla (Philips Healthcare, The Netherlands) scanner with gradients of highest width and going back up time respectively of 80 mT/m and 200 mT/m/ms. An eight-element wraparound SENSE sensitivity encoding torso-array coil was set at the front and back of the thorax for the reception of the signal. A 20 Gauge cannula-needle was set in a vein of the arm and connected to an electronic injector (MR Spectris; Medrad; Pittsburgh, Pa). After obtaining "scout" images, the MRA with high temporal resolution was performed.

In order to perform the tests a specific exam card was worked out. The 3D dynamic IT weighted gradient -echo sequences were divided to obtain a first set of data consisting of a 3D axial sequence with high temporal resolution gradient-echo, not contrasted with breath-hold, followed by a 2D IT weighted gradient-echo with free breath axial sequence, that was used to visualize the arrival of the gadolinium-DTPA bolus in the right ventricle; 4 ml of gadolinium-DTPA (Magnevist, Bayer) were injected with a 4 ml/sec flow, followed by 20 ml of physiological solution for lavage with the same flow. The mean delay for the passage of the contrast medium from the anti-cubital vein of the arm to the right ventricle was 8±3 seconds (range 5 - 11 seconds). An T1-weighted 3D dynamic sequence was used with the following parameters: TR 2.6 ms, 1.3 ms, flip angle 10°, Sense factor 2, Turbo Factor 40, EPI factor 1, Thickness 10, gap -5, (Matrix 124 x 256, FOV 435, RFOV 75%). 20 dynamics with held breath were performed for totally 20 sec of global acquisition.

**Data Processing.** Data were processed with a "Forum View workstation" Philips Achieva Intera 3T (Philips Healthcare, The Netherlands) by two radiologists expert in MR diagnostics, not informed about the patients' clinical conditions, on the basis of their consent. Signal intensity- versus-time (Si/t) curves were taken during a cardiac cycle (first bolus pass) by ROIs set in the 1st order branches of the pulmonary arteries (Figure 1 a-b). The mean number of ROIs included in the analysis for each subject varied from 6 to 10 (mean 7.33). The hemodynamic parameters taken from the signal intensity - versus -time curves were MTT and TTP.

MTT was defined as the difference between the mean time of arrival of the contrast medium and the centre of the area subtended by the signal intensity-versus-time curve. TTP was defined as the period passed between the initial moment and that of peak of the signal intensity. In order to obtain a single mean value of the hemodynamic parameters (mMTT and mTTP) for every patient, the average of the value of the MTT and TTP parameters was worked out, taken from the signal-versus-time curves, calculated for each ROI.

**Statistic Analysis.** The data of IPF patients were compared with healthy control subjects with reference to MTT and TTP by using the non-parametric Mann-Whitney test. The correlation between MTT and TTP with mPAP and IRVP was evaluated by non-
parametric Spearman test. To establish the independence of MTT and TTP values in comparison with mPAP and IRVP a multiple linear regression analysis was done.

A 'p' value lower than 0.05 was considered significant. Data were expressed as mean value±standard deviation (SD). Statistic analyses were worked out by a commercial available software (Graph-pad Prism 5, San Diego, CA).
Fig. 1: Fig. 1 ROIs positioning in the 1st order branches of the pulmonary arteries.

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Fig. 2: Comparisons of MR angiography-derived (a) mMTT and (b) mTTP of first-order pulmonary arteries between patients with IPF and control subjects. Median, range, and interquartile range values are shown. Significant differences (P < 0.001) in mMTT and mTTP were observed. The line inside each box represents the median value. The ends of the vertical lines represent minimal and maximal data values. The upper hinge of each box represents the 75th percentile of the data set. The lower hinge of each box indicates the 25th percentile.

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Fig. 3: Fig. 3 Plots show Spearman correlations: (a) mPAP versus mean TTP (mTTP), (b) mPAP versus mean MTT (mMTT), (c) PVRI versus mean TTP, and (d) PVRI versus mean MTT.

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Results

In all IPF patients the measurement of the index of pulmonary pressure by RHC was successfully performed: mPAP was 31.17±5.96 mmHg (range 20 - 39 mmHg), mPVRI was 228.9±46.33 (range 146 - 301).

Dynamic MR angiograms of the pulmonary circle were successfully acquired in all participants to the research and allowed a clear visualization of the vascular structures.

mMTT and mTTP were significantly prolonged in IPF patients compared with those of the control subjects: [mMTT, 42.97±7.55 (95% CI = 40.38 - 5.56) vs 11.31±5.15 (CI 95% = 9.54 to 13.08); mTTP, 46.23±8.36 , (95% CI = 43.36 - 49.10 ) vs 16.57±5.35 (95% CI = 14.73 - 18.41)] (p<0.001 , with medians significantly different - p < 0.05) (Figure 2a-b).

A significant crossed correlation was observed through Spearman non-parametric correlation between mTTP and mMTT with mPAP and PVRI : mPAP vs mTTP p <0.001, Spearman r = 0.6957 95%C.I. 0.4638 - 0.8384 ; mPAP vs mMTT p < 0.001, Spearman r = 0.6604 95% C.I. 0.4109 to 0.8178 ; PVRI vs mTTP p < 0.001, SPearman r = 0.6767 95% C.I. 0.4351 to 0.8274 ; PVRI vs mMTT p < 0.001 Spearman r = 0.6593, 95%C.I. 0.4094 to 0.8172 (Figure 3 a-b-c-d).

A multi-varied analysis was performed to establish which one between mPAP and IRVP contributes in a significant way to determinin neie the values of mMTT and mTTP. PVRI presented a stronger correlation than mPAP with mMTT and mTTP, though the difference was not statistically significant.

DISCUSSION

We measured MTT and TTP of the 1st order branches of the pulmonary arteries in patients with IPF, by using HTR-MRA. MTT and TTP were significantly increased in IPF patients compared with the values of healthy control subjects and they were directly correlated with PVRI and mPAP. PVRI is an useful parameter to evaluate potential pathologies of the small pulmonary vessels. In IPF patients the increase of PVRI might reflect both the presence of hypoxia (reduced concentration of blood oxygen), and the reduction of the capillary bed, following emphysema and fibrosis [7]. In fact, in patients with hypertensive pulmonary pathology morphologic alterations of the vessel wall were showed, as alterations and reduction of the "compliance" of the segmental arteries and responses to vasodilators, [9]. The progressive increase of MTT and TTP values measured with that of PVRI, as observed in the research, might reflect these morphologic alterations. Our data show that mPAP and PVRI are independently correlated with MTT and mTTP. However, TTP may be more affected by cardiac functionality compared with MTT, that may be considered strictly depending on vascular resistances evaluated by PIC.
The first studies about MR applied to pulmonary hypertension had focused their attention on the alterations of parenchymal perfusion. Several authors observed a significant correlation between the parameters of perfusion and invasive measurements of pulmonary pressure. Ohno et al first demonstrate that perfusional dynamic 3D MR allows a quantitative evaluation of the anomalies of the regional pulmonary perfusion in subjects with increased pulmonary pressure [19]. However many studies about pulmonary perfusion evaluated primitive pulmonary hypertension or secondary pulmonary hypertension in patients with chronic pulmonary thrombus-embolism or with chronic obstructive pulmonary disease (COPD). In the COPD group of patients the evaluation of the parenchymal perfusion seems to be possible as there is not a significant alteration of the parenchymal architecture and the possible loss of signal recorded may reveal alterations of the small peripheral vessels. As was suggested in a previous study [18] the increase of the parenchymal density in patients with pulmonary fibrosis, might be responsible for the reduction or the increase of the signal and might make the measurement of the perfusion difficult, though patients with IPF present a minor architectural distortion due to fibrosis with respect to patients with associated emphysema (Combined pulmonary fibrosis with emphysema - CPFE), and develop pulmonary hypertension less frequently.

The angiographic technique described in our study, which allows to acquire high temporal resolution images of pulmonary circulation from which functional information about the pulmonary circle may be obtained, might become an useful diagnostic tool also for the management of patients with pulmonary hypertension following IPF. In fact, also in this patients, parameters as MTT and TTP measured on the 1st order branches of pulmonary arteries may supply information about the functional state of the pulmonary circulation. An advantage of this technique is the reduced quantity of contrast medium necessary to data acquisition. In keeping with previous studies [18, 20], we used just a 4 ml quantity of gadolinium DTPA, that can be injected in 1 second. Phase contrast MR imaging has been developed for the measurement of pulmonary arterial flow. Nevertheless the method requires a long preparatory phase before proceeding to the execution to determine the localization of pulmonary arteries accurately. Moreover phase contrast imaging includes separate acquisitions for each lung [21, 22]. High temporal resolution MR imaging of pulmonary circulation by "scanner", working with 3.0 Tesla as previously described, is able to draw the pulmonary circulation in detail [18, 20]. Furthermore, the SENSE technique (sensitivity encoding) can be used in order to increase the acquisition speed [18]. The main advantage of MR imaging with 3.0 Tesla is the extension of SNR that increases in an approximately linear way with the intensity of the magnetic field. In fact Willinek et al. and Campeau demonstrated that the highest signal/noise ratio, obtainable by 3.0 Tesla MR scanner, is an important element to increase space resolution and it might improve the visualization of smaller vascular segments [23]. In our research SNR was used as a guide for the optimal placement of ROIs, to minimize non-uniformity of noise inside the visual field, as potential consequence of the parallel acquisition technique.
Conclusion

HTR-MRA supplies functional information about pulmonary hemodynamics in IPF patients and might have a potential significance in the evaluation and stratification of patients with pulmonary hypertension.

Nevertheless further researches with larger cohorts of patients are necessary to establish its diagnostic accuracy in patients with PH due to IPH and in other secondary forms of PH.
References


