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Abnormalities in high-resolution computed tomography of the lungs in patients with idiopathic pulmonary arterial hypertension — correlation with haemodynamic parameters and prognostic significance

Abstract

Introduction: The risk stratification in idiopathic pulmonary arterial hypertension (IPAH) patients is currently based on haemodynamic and functional parameters as well as serum biomarker concentrations. Until now the importance of changes appearing in high-resolution computed tomography (HRCT) of the lungs of patients with IPAH has not been investigated.

Material and methods: Lung HRCT scans were analysed retrospectively in 48 IPAH patients (patients): 37 women, 11 men, mean age 41 ± 15 years.

Results: Focal ground-glass opacifications (FGG) were found in 12 patients (25%), and centrilobular nodules (CN) were found in 8 patients (17%). In the remaining 58% of patients HRCT revealed no changes (N). Significantly lower stroke volume was found in the CN group (41.0 ± 8.5 ml) compared to 60.8 ± 15.1 ml in the FGG group and 58.1 ± 18.0 ml in the N group (p = 0.03). Right atrial pressure was significantly higher in the CN group (12.2 ± 4.86 mm Hg) than in the FGG group (6.9 ± 3.9 mm Hg) and the N group (7.6 ± 5.3 mm Hg), p = 0.047. The presence of nodules was combined with considerably increased risk of death, both in univariate analysis (HR 5.35, 95% CI: 1.16–24.7, p = 0.03) and in multivariate analysis (HR 6.98, 95% CI: 1.41–34.59, p = 0.02). Ground-glass opacifications correlated neither with haemodynamic nor functional indexes, and were of no prognostic significance.

Conclusions: The presence of centrilobular nodules in lung HRCT scans of IPAH patients was combined with more severe haemodynamic compromise and was an independent negative prognostic indicator.

Key words: idiopathic pulmonary arterial hypertension, high resolution computed tomography, prognosis


Introduction

Chest computed tomography (contrast-enhanced spiral CT and high-resolution CT/HRCT), is a very useful method for differential assessment of pulmonary hypertension [1, 2]. Contrast-enhanced spiral CT allows for the detection of filling defects of the pulmonary arteries caused by thrombi or external compression. HRCT scans identify patients with lung parenchyma pathology, e.g. interstitial fibrosis, underlying pulmonary hypertension [1, 2]. Chest CT is an essential test in establishing diagnosis of idiopathic pulmonary arterial hypertension (IPAH), which is made by elimina-
ting other types of pulmonary hypertension [1, 2]. The influence of IPAH on lung HRCT pictures still remains unclear. It is known that IPAH can cause lung attenuation inhomogeneity in the form of ground-glass opacifications or centrilobular nodules [3, 4]. Until now, the relation between these findings and parameters of pulmonary function testing (PFT), blood gases, haemodynamic indexes, clinical picture, and survival in IPAH patients has not been the subject of investigation.

**Material and methods**

The study population consisted of 48 IPAH patients who were hospitalized in the Department of Chest Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw during the period 1998–2006. Diagnosis of IPAH was based on finding mean rest pulmonary artery pressure > 25 mm Hg measured directly, and on simultaneous exclusion of known causes of pulmonary hypertension [1, 2]. Review of chest CT was part of a retrospective study the main goal of which was to determine abnormalities occurring in PFT of IPAH patients. Chest HRCT examinations were performed in the Radiology Department of the Institute between February 1998 and August 2006. Until April 2003 scans were obtained with a single-row helical unit Picker PQ 2000 (Siemens), and subsequently with a multi-row Somatom Sensation 16 (Siemens). All images were reassessed by an experienced radiologist in order to detect pulmonary changes.

From the patients’ medical records we extracted the results of several tests: PFT, pulmonary artery and right heart catheterization, arterialised capillary blood gases, six-minute walking distance (6MWD), and clinical parameters: WHO functional class, data regarding IPAH duration at the time of CT as well as data on patients’ survival. Haemodynamic data were available for 37 (77%) patients. Mean interval between cardiac catheterization and chest HRCT was 31 ± 37 days, and between HRCT and PFT 15 ± it was 19 days. All patients had spirometry and whole body plethysmography including measurement of bronchial resistance. Single-breath diffusion capacity for carbon monoxide (corrected for haemoglobin levels) was measured in 45 patients, and static lung compliance in 33 patients. Values corresponding with the 5th percentile of the predicted value (pred) [5] were used as lower limits of normal (LLN). An RV/TLC cutoff value of 103.88% pred was identified by ROC analysis (AUC [area under curve] 0.59, 95% CI: 0.40–0.78) as the best prognostic discriminator.

A database and all analyses were performed using STATISTICA 6.0 (Statsoft) computer software. The results are expressed as mean values ± standard deviation (SD) unless otherwise stated. For comparison of categorical variables between groups, the Pearson’s chi-square test was used. For continuous variables one-way analysis of variance (ANOVA) or its nonparametric equivalent (Kruskal-Wallis test) were applied, depending on the character of distribution, followed by post-hoc tests: Tukey’s test or multiple comparisons of mean ranges for all groups when the F value was statistically significant. Survival analysis for the whole studied group was performed using the Kaplan-Meier method. The survival time was calculated from the day of chest HRCT until the end of follow-up, which was determined as: 8 January 2007 for patients still alive on that day, the date of last contact for patients lost to follow-up, the date of lung transplantation, or the date of the patient’s death. Survival in the groups was compared with Cox-Mantel test. The prognostic value of selected variables was tested by univariate and multivariate Cox proportional hazards regression analysis. P ≤ 0.05 was considered statistically significant.

**Results**

Lung HRCT assessment was carried out in 48 IPAH patients — 37 women and 11 men, mean age 41 ± 15 years. In 12 patients (25%) focal ground-glass opacifications (FGG) were found. In 8 cases they had irregular patchy distribution (fig. 1A) and in a further 4 patients they covered bilaterally peripheral areas (fig. 1B). In 8 patients (17%) centrilobular nodules (CN) were present (fig. 1C). In half of the scans the CNs were localized regularly in the whole of the lungs, and in the other half they were distributed in an irregular manner. There were no cases of coexisting FGG and CN. In the remaining 58% of patients HRCT revealed no changes (N).

Demographic, clinical, and haemodynamic data at the time of lung HRCT for the whole study group and for subgroups depending on the HRCT findings are shown in table 1. There were no significant differences between distinguished groups in terms of: age, disease duration, frequency of nicotinism, or functional status, whereas some evident differences in haemodynamic parameters were revealed. Significantly higher right atrial pressure was found in the CN group (12.2 ± 4.86 mm Hg) compared to 6.9 ± 3.9 mm Hg in the FGG group, and 7.6 ± 5.3 mm Hg in the N group (fig. 2A). Stroke volume was significantly lower in the CN group (41.0 ± 8.5 ml) than in the FGG (60.8 ± 15.1 ml) and N (58.1 ± 18.0 ml) groups (fig. 2B).

Mean values of PFT, arterialised capillary blood gases, and six-minute walk test parameters for the whole study group and for subgroups depen-
...No significant differences regarding these variables were demonstrated.

Mean follow-up period was 38 ± 23 months (range 1.5 months–8.2 years). During this time 13 patients died, 3 patients underwent lung transplantation (those were treated as censored observations), and 1 patient was lost for follow-up after 11 months. The cumulative survival rates at 1, 2, 3, and 5 years were 98% (95% CI: 94–100%), 95% (95% CI: 89–100%), 89% (95% CI: 78–99%), and 59% (95% CI: 38–80%), respectively.

Survival time according to the HRCT picture is shown in figure 3. CN patients had significantly worse survival in reference to the N group.

The unfavourable prognostic value of centrilobular nodules was confirmed by univariate analysis; other negative prognostic factors were: lower cardiac output (evaluated at first cardiac catheterization), lower pO2 and satO2 of arterialised capillary blood, exercise desaturation > 5%, VC < LLN, FEV1 < LLN, RV/TLC > 103.88% pred and VA/TLC < 0.85. Parameters of significant prognostic value are summarized in table 3.

Among the parameters identified above, the most significant independent effect on survival in multivariate analysis was found for: RV/TLC > 103.88% pred, pO2 < 60 mm Hg and the presence of centrilobular nodules (tab. 4).

**Discussion**

In 20 of the 48 studied patients changes in lung HRCT scans in the form of ground-glass opacifications (12 cases) or centrilobular nodules (8 cases) were found.

Both ground-glass opacifications and centrilobular nodules are non-specific changes [4, 6]. Centrilobular nodules are structures connected to centrilobular arterioles or bronchioles [4, 7] corresponding with various types of histological pictures depending on...
disease entity [4]. Most probably, in arterial pulmonary hypertension, they are cholesterol granulomas resulting from either recurrent pulmonary haemorrhage or altered surfactant metabolism [8].

The presence of centrilobular nodules in lung HRCT scans of studied IPAH patients was combined with more severe haemodynamic compromise and was an independent negative prognostic indicator. It was associated with about a sevenfold increased risk of death. In none of the HRCT pictures were further changes such as thickened interlobular septa, pleural or pericardial effusion, or mediastinal adenopathy (sug-
gesting pulmonary hypertension with predominant pulmonary capillary and venous involvement [9–11] present. The isolated presence of centrilobular nodules seemed to indicate a subtype of IPAH combined with particularly poor prognosis. However, the small number of studied cases and lack of histopathological examination do not allow for a definite conclusion.

The finding of focal ground-glass opacifications was slightly more frequent than that of centrilobular nodules. Ground-glass opacification usually reflects affection of the air spaces, interstitium, or both these compartments [12]. This can be the result of alveolar or interstitial oedema, an inflammatory process, or alveolar haemorrhage [4, 6]. Interstitial oedema in the course of IPAH may be caused by fluid retention related to heart failure or elevated pressure in the pulmonary arteries. In the studied population ground-glass opacifications correlated neither with

### Table 2. Mean values (+/− standard deviation) of PFT, arterialised capillary blood gases and six-minute walk test parameters for the whole study group and for subgroups depending on lung HRCT findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Whole group</th>
<th>CN group</th>
<th>FGG group</th>
<th>N group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC% pred.</td>
<td>108.8 (15.9)</td>
<td>56.8 (8.8)</td>
<td>110.2 (14.4)</td>
<td>109.9 (15.7)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁% pred.</td>
<td>96.9 (16.3)</td>
<td>87.8 (16.2)</td>
<td>92.9 (15.3)</td>
<td>99.5 (13.5)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁/VC (%)</td>
<td>96.1 (8.7)</td>
<td>96.0 (8.7)</td>
<td>92.3 (9.2)</td>
<td>97.7 (8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>MMEF% pred.</td>
<td>70.4 (23.8)</td>
<td>68.8 (26.3)</td>
<td>62.3 (23.5)</td>
<td>74.5 (23.1)</td>
<td>NS</td>
</tr>
<tr>
<td>PEF% pred.</td>
<td>97.3 (22.1)</td>
<td>93.5 (23.1)</td>
<td>94.8 (20.8)</td>
<td>99.5 (22.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Rtot [kPa<em>s</em>L⁻¹]</td>
<td>0.2 (0.1)</td>
<td>0.2 (0.1)</td>
<td>0.2 (0.1)</td>
<td>0.3 (0.1)</td>
<td>NS</td>
</tr>
<tr>
<td>RV% pred.</td>
<td>114.5 (27.9)</td>
<td>106.8 (23.1)</td>
<td>123.4 (25.5)</td>
<td>112.8 (29.9)</td>
<td>NS</td>
</tr>
<tr>
<td>TLC% pred.</td>
<td>108.2 (14.9)</td>
<td>102.8 (12.7)</td>
<td>110.9 (15.4)</td>
<td>108.6 (15.3)</td>
<td>NS</td>
</tr>
<tr>
<td>RV/TLC% pred.</td>
<td>103.2 (17.5)</td>
<td>104.6 (21.0)</td>
<td>109.0 (15.2)</td>
<td>100.3 (17.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Cst% pred.</td>
<td>84.1 (21.1)</td>
<td>82.3 (17.7)</td>
<td>83.9 (26.5)</td>
<td>84.8 (20.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Pst% pred.</td>
<td>69.5 (19.4)</td>
<td>65.3 (24.9)</td>
<td>61.7 (18.2)</td>
<td>74.1 (17.6)</td>
<td>NS</td>
</tr>
<tr>
<td>DLco% pred.</td>
<td>69.5 (20.1)</td>
<td>63.9 (15.8)</td>
<td>66.4 (13.2)</td>
<td>72.5 (23.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Kco% pred.</td>
<td>73.2 (19.3)</td>
<td>68.9 (17.7)</td>
<td>69.9 (13.2)</td>
<td>75.7 (22.3)</td>
<td>NS</td>
</tr>
<tr>
<td>VA/TLC</td>
<td>0.9 (0.1)</td>
<td>0.9 (0.1)</td>
<td>0.9 (0.1)</td>
<td>0.9 (0.1)</td>
<td>NS</td>
</tr>
<tr>
<td>pO₂ [mm Hg]</td>
<td>66.3 (14.8)</td>
<td>66.4 (17.5)</td>
<td>63.9 (12.8)</td>
<td>67.2 (15.2)</td>
<td>NS</td>
</tr>
<tr>
<td>pCO₂ [mm Hg]</td>
<td>31.4 (4.2)</td>
<td>30.9 (4.1)</td>
<td>32.0 (5.2)</td>
<td>31.3 (3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>92.7 (4.4)</td>
<td>92.2 (5.9)</td>
<td>92.7 (4.1)</td>
<td>92.9 (4.2)</td>
<td>NS</td>
</tr>
<tr>
<td>6MWT distance [m]</td>
<td>363.9 (107.1)</td>
<td>416.1 (76.3)</td>
<td>354.8 (122.0)</td>
<td>352.1 (106.0)</td>
<td>NS</td>
</tr>
<tr>
<td>6MWT desaturation (%)</td>
<td>6.2 (8.4)</td>
<td>5.5 (5.2)</td>
<td>5.5 (5.2)</td>
<td>6.2 (11.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

CN — centrilobular nodules, FGG — focal ground glass, N — no changes, VC — vital capacity, FEV₁ — forced expiratory volume in one second, MMEF — maximal midexpiratory flow, PEF — peak expiratory flow, Rtot — total resistance, RV — residual volume, TLC — total lung capacity, Cst — static lung compliance, Pst — lung recoil pressure, DLco — diffusion lung capacity for carbon monoxide, Kco — carbon monoxide diffusion coefficient, VA — alveolar volume, pred — predicted value, pO₂ — arterialised capillary blood oxygen tension, pCO₂ — arterialised capillary blood carbon dioxide tension, SaO₂ — arterialised capillary blood oxygen saturation, NS — not significant.

![Figure 3. Survival time according to HRCT picture (*p for difference between CN and N groups). N — no HRCT changes, FGG — focal ground-glass opacification, CN — centrilobular nodules](image-url)
PFT and haemodynamic nor with functional indexes, and were of no prognostic significance.

It may sometimes be difficult to discriminate between a ground-glass opacification and the phenomenon of mosaic perfusion (fig. 1D) seen in lung HRCT scans of patients with thromboembolic or small airway disease [4, 13]. Both ground-glass opacifications and mosaic perfusion reflect patchy density differences of the lung parenchyma. Foci of ground-glass opacification correspond to pathologically changed areas of higher than is healthy tissue density. Mosaic perfusion can be the effect of disturbances of pulmonary perfusion as well as of lung ventilation. In thromboembolic pulmonary hypertension, pulmonary parenchyma has increased radiolucency (lower density) in underperfused areas with narrowed vessels, whereas correctly perfused areas have higher density and wider vessels. The diameter of pulmonary vessels differentiates between mosaic perfusion and mosaic attenuation patterns appearing in pulmonary oedema, infiltrative diseases, or alveolar haemorrhage as ground-glass opacifications. In lower respiratory tract diseases, mosaic perfusion results from ventilation disturbances, and the presence of air-trapping seen on expiratory HRCT scans is helpful in identifying this state [4].

Ground-glass opacifications and centrifilobular nodules can accompany the diseases caused by tobacco smoking [4, 6, 7]. In the studied group no significant differences were revealed in the percentage of cigarette smokers between the group with chest HRCT changes and the group without them. Moreover, no other typical smoking-related features (e.g. bronchiectasis or tree-in-bud opacities [4, 7]) were exhibited in HRCT images of cigarette smokers.

The observations presented above prove that chest HRCT is not only a useful tool in establishing IPAH diagnosis but may also have also a prognostic potential enabling the identification of patients with higher risk of an unfavourable disease course. The present study is a pioneer work and requires further investigation. There are a lot of questions waiting for answers, e.g. when, in the course of IPAH, do the above-described lung parenchyma changes appear, can they regress or progress, and what kind of microscopic picture they reflect? To answer them, further prospective studies with serial assessment of lung HRCT examinations in a larger population of IPAH patients are needed.

### References