Spleen Size in Idiopathic and Heritable Pulmonary Arterial Hypertension

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Key Words
Outcome assessment • Pulmonary arterial hypertension • Spleen • Splenomegaly

Abstract

Background: It is unknown whether the spleen size correlates with disease severity and outcome in patients with idiopathic and heritable pulmonary arterial hypertension (PAH). Objectives: To determine the prevalence of splenomegaly in PAH and assess whether it correlates with severity of disease and outcome. Methods: We identified subjects with either heritable or idiopathic PAH who had Doppler echocardiography, right-heart catheterization and computed tomography (CT) of the chest and/or abdomen that included the spleen. Results: We included 62 subjects with a mean age (±SD) of 49 (±15) years; 82% were women. Spleen dimensions were 10 (±3), 6 (±2) and 9 (±2) cm for the cranio-caudal length, thickness and width measurements, respectively. The median [interquartile range (IQR)] spleen volume was 344 (225–533) cm³. Splenomegaly was observed in 52–63% of the patients, depending on the formula used. The spleen volume was not associated with clinical, echocardiographic or hemodynamic variables. Spleen volume was not associated with adjusted mortality. We studied the characteristics of the spleen during autopsy in 9 patients with idiopathic PAH who died of right-heart failure. The mean (IQR) spleen weight was 220 (151–325) g. We observed early congestion in all but 2 patients who had chronic congestion. Conclusions: Splenomegaly of predominantly mild degree is common in idiopathic and heritable PAH. However, spleen size was not associated with clinical, echocardiographic, hemodynamic and survival data in these patients.

Introduction

Pulmonary arterial hypertension (PAH) is a disease characterized by restrictive flow through the pulmonary circulation that can lead to right-heart failure and death [1]. It involves a variety of diseases included in group I of the 4th World Symposium on Pulmonary Hypertension updated in 2008 [2]. PAH is hemodynamically characterized by a mean pulmonary arterial pressure ≥25 mm Hg with pulmonary vascular resistance (PVR) ≥3 Wood units and pulmonary arterial occlusion pressure ≤15 mm Hg [1]. When the right ventricular (RV) compensatory response to the increased PVR is overwhelmed, right heart failure ensues. Clinical manifestations of right
heart failure include symptoms and signs resulting from venous congestion and low cardiac output [3]. Characteristic physical signs related to venous congestion include hepatomegaly, ascites and peripheral edema [4, 5]. Splenomegaly has been associated with right heart failure [6], but it is usually not described as part of the signs observed in patients with advanced PAH [7, 8].

It is unknown whether patients with idiopathic or heritable PAH have abnormal spleen volume and whether its volume correlates with clinical, echocardiographic and hemodynamic parameters or outcomes. We hypothesized that patients with idiopathic and heritable PAH have splenomegaly which may correlate with severity of disease and outcomes. We evaluated whether assessing the spleen volume in the chest CT could provide valuable prognostic information in these patients.

**Methods**

**Study Design and Inclusion Criteria**

This study was approved by the Cleveland Clinic Institutional Review Board (protocol number: 10-1127). Informed consent was waived. We identified subjects using the Cleveland Clinic Pulmonary Hypertension Registry. We selected patients with pulmonary arterial occlusion pressure ≤15 mm Hg, PVR ≥3 Wood units, forced expiratory volume in 1 s/forced vital capacity (FVC) ≥0.6, and total lung capacity ≥60%. Of those, we only included patients with either idiopathic or heritable PAH (n = 140) [2] who had a CT of the chest (including the spleen) or abdomen between 1994 and 2010.

Each patient underwent a careful selection process to exclude other etiologies of pulmonary hypertension. We excluded all patients in whom at least two pulmonary hypertension physicians were not in complete agreement about the diagnosis of idiopathic or heritable PAH. Except for 1 patient who had splenectomy and was excluded, no other patient had any medical condition linked to changes in the spleen volume.

**Measurements and Calculations**

We selected the CT scans of the chest and abdomen that incorporated the spleen in its entirety and were performed closest in time to any right-heart catheterization (RHC) performed at our institution. In the case of several studies, we selected the first one. Studies were obtained with commercially available single- and four-slice CT scanners using a slice thickness of 5 mm at 4-mm intervals before 2003. Since 2004, studies were obtained initially with 16- and subsequently with 64-detector CT scanners using 5-, 3- and 1-mm section thicknesses at 2.5-, 1.5- and 1-mm intervals, respectively. Two radiologists (R.Y. and A.G.) reviewed all the CT scans performed in these patients.

We measured the splenic length, width and thickness in all patients. The length was obtained by multiplying the number of sections where the spleen was visualized by the thickness of the spleen. White double-headed arrows mark the splenic measurements.
Spleen Size in Pulmonary Hypertension

**Results**

**Patient Characteristics**

We included 62 unique subjects (82% women) with a mean age (±SD) of 49 (±15) years. Fifty-four had idiopathic and 8 had heritable PAH. Race was Caucasian in 81%, African American in 15% and other in 4%. New York Heart Association (NYHA) functional class was II in 36%, III in 48% and IV in 16% of the patients. Mean (SD) height was 1.62 (±8.5) m, weight 77 (±23) kg and mean body mass index was 29 (±8). Six patients (10%) were receiving PAH-targeted therapy at the time of the chest/abdomen CT, 3 patients sildenafil, and 3 bosentan. Brain natriuretic peptide was 424 (±592) pg/ml and the 6-min walk distance was 327 (±104) m or 58.5% (±17) of predicted [13]. Hemodynamic and echocardiographic characteristics are shown in tables 1 and 2, respectively.

**Indications for CT**

CT of the chest/abdomen was performed with a median (IQR) difference from the RHC of 0 (0–6) months. A total of 53 (86%) CT scans were of the chest and the rest of the abdomen (9 patients, 14%). CT were done for further evaluation of lung parenchyma (47%), dyspnea (19%), abdominal distension (9%), evaluation before lung transplantation (7%), lung nodule assessment (7%), and for other reasons (11%) such as research, chest pain, and follow-up of ovarian carcinoma.

**CT Measurements**

The aorta and pulmonary artery diameters were 3 (±0.5) and 3.4 (±0.5) cm, respectively; with a ratio of pulmonary artery/aorta of 1.2 (±0.2). Spleen dimensions were 10 (±3), 6 (±2), and 9 (±2) cm for the craniocaudal,
thickness and width measurements, respectively. The median (IQR) splenic index was 541 (337–868) cm$^3$. Sixty percent of the patients had a splenic index above the upper limit of the normal range (480 cm$^3$) [16, 17]. The median (IQR) splenic volumes measured by Prassopoulos et al. [9] and prolate ellipsoid volume [10] formula were 344 (225–533) and 283 (176–455) cm$^3$, respectively (fig. 2).

The splenic volumes measured by the formula of Prassopoulos et al. [9] were 339 (222–291) and 378 (279–553) cm$^3$ in patients that underwent CT of the chest and abdomen, respectively (p = 0.39). The spleen size was directly associated with weight (R = 0.43, p = 0.001) but not with age and height. The splenic size was higher in males [461 (339–673) cm$^3$] than in females [333 (218–491) cm$^3$; p = 0.021, Mann-Whitney test]. In multivariate analysis that included weight and gender, only weight was significantly associated with spleen size (p = 0.027).

Using the table for spleen volume suggested by Sprogøe-Jakobsen and Sprogøe-Jakobsen [11], splenomegaly was observed in 63% of the patients using the formula to calculate volume of Prassopoulos et al. [9] and 51.6% of the individuals by applying the formula to calculate the volume of a prolate ellipsoid [10]. Only 1 patient (1.6%) had hyposplenia (<5% limit for spleen size CI) by

### Table 1. Hemodynamic parameters in all the patients, with or without splenomegaly (means ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n = 62)</th>
<th>No splenomegaly (n = 22)</th>
<th>Splenomegaly (n = 39)</th>
<th>p value (Welch’s t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP, mm Hg</td>
<td>12 ± 7</td>
<td>10 ± 5</td>
<td>13 ± 7</td>
<td>0.08</td>
</tr>
<tr>
<td>RV systolic pressure, mm Hg</td>
<td>83 ± 22</td>
<td>85 ± 20</td>
<td>82 ± 23</td>
<td>0.6</td>
</tr>
<tr>
<td>RV diastolic pressure, mm Hg</td>
<td>14 ± 10</td>
<td>13 ± 7</td>
<td>15 ± 11</td>
<td>0.39</td>
</tr>
<tr>
<td>PA systolic pressure, mm Hg</td>
<td>86 ± 21</td>
<td>87 ± 21</td>
<td>85 ± 22</td>
<td>0.75</td>
</tr>
<tr>
<td>PA diastolic pressure, mm Hg</td>
<td>37 ± 11</td>
<td>39 ± 12</td>
<td>37 ± 11</td>
<td>0.61</td>
</tr>
<tr>
<td>PA mean pressure, mm Hg</td>
<td>54 ± 14</td>
<td>55 ± 14</td>
<td>53 ± 14</td>
<td>0.66</td>
</tr>
<tr>
<td>PAOP, mm Hg</td>
<td>10 ± 4</td>
<td>10 ± 4</td>
<td>10 ± 4</td>
<td>0.96</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>4.1 ± 1.5</td>
<td>3.8 ± 1.4</td>
<td>4.2 ± 1.5</td>
<td>0.28</td>
</tr>
<tr>
<td>Cardiac index, l/min/m$^2$</td>
<td>2.2 ± 0.8</td>
<td>2 ± 0.6</td>
<td>2.3 ± 0.8</td>
<td>0.13</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>12 ± 7</td>
<td>13 ± 7</td>
<td>12 ± 7</td>
<td>0.85</td>
</tr>
<tr>
<td>TPG, mm Hg</td>
<td>43 ± 14</td>
<td>44 ± 14</td>
<td>43 ± 14</td>
<td>0.8</td>
</tr>
</tbody>
</table>

PA = Pulmonary artery; PAOP = PA occlusion pressure; RAP = right atrial pressure; TPG = transpulmonary gradient. Splenomegaly was defined by a volume (using the Prassopoulos et al. [9] formula) higher than the 95% limit according to the expected spleen volume by height and weight described by Sprogøe-Jakobsen and Sprogøe-Jakobsen [11].

### Table 2. Echocardiographic parameters in all patients, with or without splenomegaly

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n = 62), n (%)</th>
<th>No splenomegaly (n = 22), n (%)</th>
<th>Splenomegaly (n = 39), n (%)</th>
<th>p value (Fisher’s exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV dilation</td>
<td>7 (11)</td>
<td>1 (4)</td>
<td>6 (15)</td>
<td>0.59</td>
</tr>
<tr>
<td>Absent</td>
<td>4 (6)</td>
<td>2 (9)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>24 (39)</td>
<td>10 (46)</td>
<td>14 (36)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>27 (44)</td>
<td>9 (41)</td>
<td>17 (44)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>8 (13)</td>
<td>1 (4)</td>
<td>7 (18)</td>
<td></td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>3 (5)</td>
<td>3 (14)</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>Absent</td>
<td>29 (47)</td>
<td>11 (50)</td>
<td>18 (46)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>22 (35)</td>
<td>7 (32)</td>
<td>14 (36)</td>
<td></td>
</tr>
</tbody>
</table>

1 One patient with hyposplenia was removed from the subgroup analysis.
the formula described by Prassopoulos et al. [9] and 2 (3.2%) by the formula used to determine the volume of a prolate ellipsoid [10] (table 3).

When using a spleen volume to define splenomegaly of 314.5 cm³, the formula by Prasspoulos et al. [9] revealed that 36 patients (58%) had splenomegaly. Using the upper 95% limit (334 cm³) from the normal spleen volume proposed by Henderson et al. [18], we observed that 34 (55%) patients had splenomegaly. If only craniocaudal splenic length is used, splenomegaly (craniocaudal length ≥ 10 cm) [19] was observed in 22 patients (36.1%).

**Correlation of CT Findings**
We did not observe a significant association between spleen volume obtained by the formula described by Prassopoulos et al. [9] and either pulmonary artery diameter ($R = 0.24$, $p = 0.09$) or pulmonary artery/aortic ratio ($p = 0.97$). Similarly, no significant associations were observed between spleen volume and NYHA functional class, laboratory data (brain natriuretic peptide serum levels, hemoglobin, white blood cells, platelets, sodium, creatinine, blood urea nitrogen, albumin, bilirubin, alkaline phosphatase, and alanine aminotransferase), pulse oximeter oxygen saturation ($\text{SpO}_2$) at rest on room air, 6-min walk distance (in meters or percent of predicted), echocardiographic (left ventricular ejection fraction, tricuspid jet velocity, or degree of RV dilation or dysfunc-
tion) or hemodynamic parameters (fig. 3). Lack of association was also observed for all these variables when splenic volume was adjusted for age, height, weight, and gender. Aspartate aminotransferase was significantly associated with splenic volume ($R = -0.33$, $p = 0.026$), although this association disappeared when adjusting for other factors ($p = 0.09$).

**Survival Analysis**
Survival at 1, 2, and 3 years was 89.7, 73.1 and 64.3%, respectively. When survival was adjusted for age, gender, height, and weight, we did not find a significant effect of spleen volume as a continuous variable (HR: 1; 95% CI: 0.997–1.002; $p = 0.74$; fig. 4). Similarly, no survival difference was noted when the binary variable splenomegaly (defined by the Sprogøe-Jakobsen and Sprogøe-Jakobsen

**Table 3. Spleen size**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenomegaly</td>
<td>39 (63)</td>
<td>32 (52)</td>
</tr>
<tr>
<td>Normal spleen size</td>
<td>22 (35)</td>
<td>28 (45)</td>
</tr>
<tr>
<td>Hyposplenia</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

1 See Materials and Methods for the definitions of these terms.

Fig. 2. Histograms of splenic volumes in idiopathic and heritable PAH using the Prassopoulos et al. [9] formula (a) and the formula for calculation volume of prolate ellipsoid [10] (b).
Autopsy Findings from Patients with Idiopathic PAH

We identified the autopsies of 9 patients with idiopathic PAH patients who died of right heart failure. None of these 9 patients had a CT of the chest or abdomen close to the RHC to be included in the main analysis. The mean (±SD) age of these patients was 44 (±20) years and 67% of them were females. Mean (±SD) height and weight were 161 (±9) cm and 69 (±11) kg, respectively. On the autopsies, the heart, and left and right lung weights were 490 (IQR: 360–605), 650 (IQR: 400–770) and 570 (IQR: 338–725) g, respectively. Pericardial and pleural effusions of at least mild degree were noted in 3 and 6 cases, respectively, and ascites in 6 patients. The liver weight was 1,650 (IQR: 1,475–1,950) g and the spleen weight was 220 (IQR: 151–325) g. Marked RV hypertrophy (0.8 cm, IQR: 0.6–1.1) and dilation was noted in all cases, as well as plexogenic pulmonary hypertensive arteriopathy on microscopic evaluation and some degree of hepatic congestion. Splenic congestion was seen in all cases, and 2 spleens revealed fibrosis of the capsule (fig. 5).
Discussion

This study demonstrates for the first time that splenomegaly, predominantly of mild degree, is common in patients with advanced idiopathic or heritable PAH. The presence of chronic congestion as the sole macro- and microscopic finding in the enlarged spleens on autopsies suggests that chronic passive congestion is likely the cause of the splenomegaly. However, the spleen volume estimated by CT showed no association with clinical, echocardiographic, or hemodynamic parameters or survival.

To the best of our knowledge, there is no available information on the spleen size in patients with idiopathic and heritable PAH. Hepatomegaly and ascites, but not splenomegaly, are frequently included as part of signs indicative of the presence of right heart failure in these patient groups [4, 20]. However, one of the common causes of splenomegaly is congestion due to heart failure. We hypothesized that as patients develop right heart failure as a result of longstanding PAH, some degree of splenomegaly would become evident.

We found that splenomegaly was common (52–63%) in patients with advanced idiopathic and heritable PAH, irrespective of the definition used. We measured the spleen volume by using two multidimensional indices [9, 10], and compared the volumes obtained with those expected for height and weight as proposed previously [11]. We defined splenomegaly when splenic volumes were above the 95% CI for height and weight. This last approach was important as in our cohort, splenic volume correlated with body weight in multivariate analysis. Interestingly, we observed that the overall increase in spleen size was modest and this is in correlation with what is seen in congestive heart failure from other etiologies [6].

Hyposplenia was rare, since only 1 or 2 patients, depending on the formula used, had this condition (fig. 1). Hoeper et al. [21] described a higher prevalence of asplenia in patients with idiopathic PAH when compared with individuals with other lung diseases who received lung transplant (11.5 vs. 0%). Fahy et al. [22] reported hyposplenia in a patient with idiopathic PAH potentially explained by splenic ischemia due to reduced cardiac output, hypoxia, and polycythemia. In our study, we did not find an association between spleen size and either cardiac output or hemoglobin concentration in the blood. In our cohort, the patient with hyposplenia had a cardiac index of 3.4 l/min/m², PVR of 6 Wood units, hemoglobin of 13.7 g/dl and $\text{SpO}_2$ at rest on room air of 98%.

We were not able to detect an association (linear or nonlinear) between splenic volume, either as a continuous or dichotomized variable, and NYHA functional class, laboratory data (including complete blood counts and comprehensive metabolic panel), 6-min walk distance, and echocardiographic or hemodynamic parameters. Similarly, splenic volume at the time of the initial CT was not associated with survival. These findings do not support the routine measurement of spleen volume during CT performed to further patients with idiopathic or heritable PAH.

As part of the present study, we collected information from autopsies performed in patients with idiopathic or heritable PAH who died of right heart failure. We observed that the spleen weight was 220 (IQR: 151–325) g, and 55 and 33% of the patients had a splenic weight ≥200 g.

Fig. 5. Pathology examination of the spleen in idiopathic and heritable PAH. Chronic congestive splenomegaly showing a thickened and fibrous capsule (a; HE, ×4), fibrotic and cellular red pulp (b; HE, ×20), dilated sinusoids (c; HE, ×20) and hemosiderin deposition from episodes of old hemorrhage (HE, ×40).
and ≥250 g, respectively (proposed cutoff points for splenomegaly) [6, 16, 23, 24]. There is significant variability in the normal spleen weight or volume [11]; hence we used different methods to define splenomegaly. The weight of the spleen differs in vivo from autopsy specimens due to blood loss during the process of extraction of the organ to be weighed [16, 17]. We also noted these differences in our study given that the in vivo spleen weight was estimated (spleenic volume x spleen specific gravity of 1.05 g/ml) at 361 (IQR: 236–560) g.

There are limitations to our study. We did not determine the spleen volume by the summation-of-volumes technique (gold standard), although spleen length and the multidimensional indices that include length, width, and thickness have shown excellent correlation with the gold standard technique [19, 25, 26]. Thus we decided to use these simpler indexes that reliably estimate splenic size instead of other labor-intensive and clinically impractical methodologies [19, 25]. We included patients (14%) in whom the splenic volume was determined in a CT of the abdomen performed for abdominal distension. This could have potentially selected a subgroup of patients with a larger spleen; however, the spleen size was similar between patients who underwent CT of the abdomen or chest, and we took precautions not to include patients with any other pathology known to affect the spleen volume.

### Conclusions

Splenomegaly of mild degree is common in patients with advanced idiopathic and heritable PAH. We did not find supportive data to routinely assess splenic volume in idiopathic or heritable PAH patients.

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