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 ($\pm$ SD) of 49 ($\pm$ 15) years; 82% were women. Spleen dimensions were 10 ($\pm$ 3), 6 ($\pm$ 2) and 9 ($\pm$ 2) cm for the craniocaudal 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 charac-

teristics 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.

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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 artery pressure $\geq$ 25 mm Hg with pulmonary vascular resistance (PVR) $\geq$ 3 Wood units and pulmonary arterial occlusion pressure $\leq$ 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

Fig. 1. Splenomegaly and hyposplenism in patients with idiopathic and heritable PAH. Splenic length, width and thickness, respectively, in a patient with splenomegaly (**a–c**) and in a subject with hyposplenism (**d–f**). White double-headed arrows mark the splenic measurements.

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 pulmo-

nary 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 $\geq 60\%$. 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

cuts. We determined splenic width as the largest diameter of the spleen on any transaxial slice, and we measured maximum splenic thickness on any section as the distance between the inner and outer borders of the spleen on a plane perpendicular to the splenic width (fig. 1). We calculated the spleen volume using the formula described by Prassopoulos et al. [9] $[(0.58 \times \text{splenic length} \times \text{splenic width} \times \text{splenic thickness}) + 30]$ and the one used to calculate the volume of a prolate ellipsoid $(0.524 \times \text{splenic length} \times \text{splenic width} \times \text{splenic thickness})$ [10]. The splenic index is the multiplication of the 3 splenic measurements without the incorporation of a correction factor.

Splenomegaly was considered if the calculated splenic volume exceeded the 95% limit for spleen size by height and weight, as described by Sprogøe-Jakobsen and Sprogøe-Jakobsen [11]. Similarly, we defined hyposplenism when the calculated splenic volume was less than the 5% limit for spleen size by height and weight [11]. Normal spleen size was considered present when the splenic volume was within the 5–95% limit interval.

RHC data were obtained from studies done as part of clinical evaluation. The procedures were performed in the standard manner in the cardiac catheterization laboratory using a 7-french pulmonary artery catheter. Pressure measurements were obtained from paper recordings at end-expiration. Cardiac output was obtained by the thermodilution method and transpulmonary gradient (mean pulmonary artery-occlusion pressure) and PVR (transpulmonary gradient/cardiac output) were calculated.

In addition, we reviewed the transthoracic Doppler echocardiogram performed the closest to the CT-RHC pair included in the analysis. Experienced operators, blinded to the results of the CT of the chest/abdomen, reviewed the echocardiograms and assessed RV size and function subjectively. A 6-min walk test was performed following American Thoracic Society guidelines [12]. Predicted 6-min walk distance was estimated using formulae suggested by Enright and Sherrill [13]. Plasma brain natriuretic peptide was measured at the time of RHC in 40 patients.

In order to support our findings, we also reviewed the reports of all autopsies performed at the Cleveland Clinic from 1990 to 2010 that included the phrases ‘primary pulmonary arterial hypertension’, ‘idiopathic pulmonary arterial hypertension’ and ‘plexiform lesions’ in any form within the text. Only the patients with idiopathic or heritable PAH who died of right heart failure were included to ensure the absence of any other condition that could result in alteration of the spleen weight. We recorded the age at the time of death, gender, height, weight, heart weight, right and left ventricular heart thickness, presence and amount of pericardial/pleural effusions and ascites, and the liver and spleen weights.

Statistics

Means and standard deviations are provided for all continuous variables when normally distributed, and medians [interquartile ranges (IQR)] when not. Two-group comparisons were performed by Welch’s *t* test or the Mann-Whitney *U* test when appropriate. Categorical data were compared using Fischer’s exact test. We used Pearson’s correlation and linear regression analysis (adjusted for age, gender, height, and weight) [14] to compare splenic volume with other continuous variables. Nonlinear relationships were assessed by fitting a LOWESS (locally weighted scatterplot smoothing) line. Survival was assessed by Kaplan-Meier methodology. Time 0 was the date at the time of the CT of

the chest/abdomen, and the end of follow-up was December, 2010, or the time of the recipient’s death (or transplantation, when a combined endpoint was used). Survival analysis was also performed with Cox proportional hazards modeling, using spleen volume and other factors as covariates, adjusted by age and gender, height, and weight. Hazard ratios (HR) and the corresponding 95% confidence intervals (CI) are shown. At the Cleveland Clinic, patients are transplanted using criteria established by the International Society for Heart and Lung Transplantation [15]. Death of the study participants was ascertained by reviewing our records and querying the US Social Security Death Index. All *p* values reported are two tailed. A value of $p < 0.05$ was considered significant. Statistical analyses were performed using the statistical package IBM SPSS, version 20 (IBM, Armonk, New York, N.Y., USA) and R statistical software, version 2.13.0 (www.r-project.org).

Results

Patient Characteristics

We included 62 unique subjects (82% women) with a mean age ($\pm$ SD) of 49 ($\pm$ 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 ($\pm$ 8.5) m, weight 77 ($\pm$ 23) kg and mean body mass index was 29 ($\pm$ 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 ($\pm$ 592) pg/ml and the 6-min walk distance was 327 ($\pm$ 104) m or 58.5% ($\pm$ 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 ($\pm$ 0.5) and 3.4 ($\pm$ 0.5) cm, respectively; with a ratio of pulmonary artery/aorta of 1.2 ($\pm$ 0.2). Spleen dimensions were 10 ($\pm$ 3), 6 ($\pm$ 2), and 9 ($\pm$ 2) cm for the craniocaudal,

Table 1. Hemodynamic parameters in all the patients, with or without splenomegaly (means $\pm$ SD)

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

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

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

¹ One patient with hyposplenism was removed from the subgroup analysis.

thickness and width measurements, respectively. The median (IQR) splenic index was 541 (337–868) cm³. Sixty percent of the patients had a splenic index above the upper limit of the normal range (480 cm³) [16, 17]. The median (IQR) splenic volumes measured by Prassopoulos et al. [9] and prolate ellipsoid volume [10] formulae were 344 (225–533) and 283 (176–455) cm³, respectively (fig. 2).

The splenic volumes measured by the formula of Prassopoulos et al. [9] were 339 (222–291) and 378 (279–553) cm³ 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) cm³] than in females [333 (218–491) cm³; 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 hyposplenism (<5% limit for spleen size CI) by

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).

Table 3. Spleen size

Formulae for splenic volume	Prassopoulos et al. [9] n (%)	Prolate ellipsoid volume [10] n (%)
Splenomegaly ¹	39 (63)	32 (52)
Normal spleen size ¹	22 (35)	28 (45)
Hyposplenism ¹	1 (2)	2 (3)

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

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 Prassopoulos 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 (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 dysfunction) 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 splenic 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 Sprogø-Jakobsen and Sprogø-Jakobsen

Fig. 3. Scatter plots with linear regression and LOWESS line. All panels have boxplots corresponding to the variable shown in the x and y axis. **a–c** Scatter plots of right atrial pressure (RAP), mean pulmonary artery pressure (PAP) and PVR versus splenic volume. All scatter plots have linear regression (solid) and LOWESS non-parametric regression line (middle broken line) with 95% confidence envelopes around the fit (external broken lines). All relationships were nonsignificant ($p > 0.05$).

Fig. 4. Cox survival analysis in patients with or without splenomegaly. Splenomegaly defined by the Sprogøe-Jakobsen and Sprogøe-Jakobsen [11] table. No statistical survival difference was observed between the groups of patients with or without splenomegaly, adjusted for age, gender, height, and weight ($p = 0.84$).

[11] table) was included in the model, adjusted for age, gender, weight, and height (HR: 0.91; 95% CI: 0.36–2.3; $p = 0.84$).

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 ($\pm$ SD) age of these patients was 44 ($\pm$ 20) years and 67% of them were females. Mean ($\pm$ SD) height and weight were 161 ($\pm$ 9) cm and 69 ($\pm$ 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).

Fig. 5. Pathology examination of the spleen in idiopathic and heritable PAH. Chronic congestive splenomegaly showing a thickened and fibrous capsule (**a**; HE, $\times 4$), fibrotic and cellular red pulp (**b**; HE, $\times 20$), dilated sinusoids (**c**; HE, $\times 20$) and hemosiderin deposition from episodes of old hemorrhage (HE, $\times 40$).

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].

Hyposplenism was rare, since only 1 or 2 patients, depending on the formula used, had this condition (fig. 1). Hoepfer 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 hyposplenism 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 hyposplenism had a cardiac index of 3.4 l/min/m², PVR of 6 Wood units, hemoglobin of 13.7 g/dl and SpO₂ at rest on room air of 98%.

We were not able to detect an association (linear or non-linear) 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

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 splenic weight was estimated (splenic volume $\times$ 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 splenic 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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References

- McLaughlin VV, Archer SL, Badesch DB, et al: ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;53:1573–1619.
- Simonneau G, Robbins IM, Beghetti M, et al: Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:S43–S54.
- Mahmud M, Champion HC: Right ventricular failure complicating heart failure: pathophysiology, significance, and management strategies. *Curr Cardiol Rep* 2007;9:200–208.
- McGoon M, Gutterman D, Steen V, et al: Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126:14S–34S.
- Dresdale DT, Schultz M, Michtom RJ: Primary pulmonary hypertension. I. Clinical and hemodynamic study. *Am J Med* 1951;11:686–705.
- Pozo AL, Godfrey EM, Bowles KM: Splenomegaly: investigation, diagnosis and management. *Blood Rev* 2009;23:105–111.
- McLaughlin VV, Archer SL, Badesch DB, et al: ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation* 2009;119:2250–2294.
- Badesch DB, Champion HC, Sanchez MA, et al: Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S55–S66.
- Prassopoulos P, Daskalogiannaki M, Raisaki M, et al: Determination of normal splenic volume on computed tomography in relation to age, gender and body habitus. *Eur Radiol* 1997;7:246–248.
- Yetter EM, Acosta KB, Olson MC, et al: Estimating splenic volume: sonographic measurements correlated with helical CT determination. *AJR Am J Roentgenol* 2003;181:1615–1620.
- Sprogøe-Jakobsen S, Sprogøe-Jakobsen U: The weight of the normal spleen. *Forensic Sci Int* 1997;88:215–223.
- ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117.
- Enright PL, Sherrill DL: Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998;158:1384–1387.
- DeLand FH: Normal spleen size. *Radiology* 1970;97:589–592.
- Orens JB, Estenne M, Arcasoy S, et al: International guidelines for the selection of lung transplant candidates: 2006 update – a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2006;25:745–755.

- 16 Cools L, Osteaux M, Divano L, et al: Prediction of splenic volume by a simple CT measurement: a statistical study. *J Comput Assist Tomogr* 1983;7:426–430.
- 17 Strijk SP, Wagener DJ, Bogman MJ, et al: The spleen in Hodgkin disease: diagnostic value of CT. *Radiology* 1985;154:753–757.
- 18 Henderson JM, Heymsfield SB, Horowitz J, et al: Measurement of liver and spleen volume by computed tomography. Assessment of reproducibility and changes found following a selective distal splenorenal shunt. *Radiology* 1981;141:525–527.
- 19 Bezerra AS, D'Ippolito G, Faintuch S, et al: Determination of splenomegaly by CT: is there a place for a single measurement? *AJR Am J Roentgenol* 2005;184:1510–1513.
- 20 Barst RJ, McGoon M, Torbicki A, et al: Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;43:40S–47S.
- 21 Hoeper MM, Niedermeyer J, Hoffmeyer F, et al: Pulmonary hypertension after splenectomy? *Ann Intern Med* 1999;130:506–509.
- 22 Fahy G, Robinson K, Deb B, et al: Primary pulmonary hypertension and functional hyposplenism. *Postgrad Med J* 1992;68:383–385.
- 23 Myers J, Segal RJ: Weight of the spleen. I. Range of normal in a nonhospital population. *Arch Pathol* 1974;98:33–35.
- 24 Sternberg S: *Histology for Pathologists*, ed 2. Philadelphia, Lippincott-Raven, 1997.
- 25 Rezai P, Tochetto SM, Galizia MS, et al: Splenic volume model constructed from standardized one-dimensional MDCT measurements. *AJR Am J Roentgenol* 2011;196:367–372.
- 26 Lamb PM, Lund A, Kanagasabay RR, et al: Spleen size: how well do linear ultrasound measurements correlate with three-dimensional CT volume assessments? *Br J Radiol* 2002;75:573–577.