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Post splenectomy related pulmonary hypertension

Atul V Palkar, Abhinav Agrawal, Sameer Verma, Asma Iftikhar, Edmund J Miller, and Arunabh Talwar

Abstract

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Splenectomy predisposes patients to a slew of infectious and non-infectious complications including pulmonary vascular disease. Patients are at increased risk for venous thromboembolic events due to various mechanisms that may lead to chronic thromboembolic pulmonary hypertension (CTEPH). The development of CTEPH and pulmonary vasculopathy after splenectomy involves complex pathophysiologic mechanisms, some of which remain unclear. This review attempts to aggregate the current evidence behind our understanding about the etiopathogenesis of pulmonary vascular disease related to splenectomy and highlight the controversies that surround its management.

**Keywords**

Pulmonary hypertension; Thalassemia; Splenectomy; Thrombocytosis; Chronic thromboembolic pulmonary hypertension

**INTRODUCTION**

The spleen plays a key role in immune homeostasis through its ability to link innate and adaptive immunity. Splenectomy predisposes the individual to a life-long increased risk of severe infections\[1\]. Besides a risk of localized or generalized infection there is also a well-known risk of thromboembolic events due to thrombocytosis post-splenectomy\[2\]. More specifically, in post-splenectomy patients there is a risk of pulmonary complications such as pneumonia, pleural effusion. Recently, there has been a growing interest about non-infectious complications such as thromboembolic events and pulmonary vasculopathies (Table 1). Pulmonary thromboembolic disease in the form of pulmonary embolism leading to chronic thromboembolic pulmonary hypertensive disease is one of the observed pulmonary complications of splenectomy. The pathophysiology of these conditions is complex and not yet clearly understood. Herein we attempt to describe the possible mechanisms of postsplenectomy pulmonary hypertension with a review of the literature.

**INDICATIONS FOR SPLENECTOMY**

There are many indications for splenectomy but the most common cause remains traumatic injury leading to rupture of the spleen. In addition there are many benign and neoplastic conditions that may lead to removal of the spleen. Hematologic causes may include autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura (ITP), hereditary spherocytosis, pyruvate kinase deficiency, glucose-6 phosphate dehydrogenase deficiency or hypersplenism\[3\]. In addition there are neoplastic conditions that warrant splenectomy such as Hodgkin’s disease, non-Hodgkin’s lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy cell leukemia and primary or metastatic tumors\[3\]. Other benign indications may be Gaucher’s disease\[4\] and Chediak-Higashi Syndrome\[5\]. Complications post-splenectomy include acute complications of general surgery that include impaired wound healing, bleeding, post surgical infection due to high dose corticosteroids or possible gastric or pancreatic fistulas. However, splenectomy may be associated with an elevated risk for cardiovascular events such as myocardial infarction and stroke\[6\]. In addition to the aforementioned complications splenectomy predisposes patients for increased thromboembolic events\[7\] and pulmonary hypertension\[8\].
PULMONARY HYPERTENSION AND SPLENECTOMY

Pulmonary hypertension (PHTN) is characterized by a mean pulmonary arterial pressure (mPAP) \( \geq 25 \text{ mmHg} \) at rest\(^9\). The World Health Organization (WHO) has proposed a classification system for pulmonary hypertension based on common clinical features (Table 2)\(^{10}\). Patients with splenectomy can develop PHTN with histopathological changes similar to those with WHO Group 1 Pulmonary Arterial Hypertension (PAH)\(^8,11\) and WHO Group 4 - Chronic Thromboembolic Pulmonary Hypertension (CTEPH)\(^{11–13}\). In addition splenectomized patients developing PHTN in the setting of hemolytic disorders, trauma, sickle cell disease, Gaucher’s disease are included in WHO Group 5 definition of pulmonary hypertension.

Initially the link between splenectomy and PHTN was suggested in patients with thalassemia and hereditary stomatocytosis\(^{12,14,15}\). It has been estimated that the time interval between splenectomy and the development of PHTN is long (range 2–35 years)\(^{8,11}\). Autopsy findings from 58 patients with thalassemia showed pulmonary vascular changes indicative of microthromboemboli in 54% splenectomized patients compared to 16% of those who had not had splenectomy\(^{14}\). In a study by Hoeper et al\(^8\) the prevalence of asplenia (including traumatic asplenia) was significantly higher (11.5%) among 61 patients with unexplained PHTN. In a study by Jaïs et al\(^{11}\) a cohort of 257 patients referred for the treatment of CTEPH, 22 patients (8.6%) had a history of splenectomy. In the control group of idiopathic PHTN in the same study, 2.5% of patients had splenectomy compared to 0.56% in patients with chronic lung conditions\(^{11}\). In another study of 134 adults with Gaucher’s disease, PHTN was diagnosed on echocardiogram in 9 patients (7%) on enzyme replacement therapy; 6 patients had prior splenectomy\(^{16}\).

An increased incidence of PHTN has also been described in patients who have undergone splenectomy for trauma\(^{8,11}\), hemolytic disorders such as thalassemia, pyruvate kinase deficiency, hereditary spherocytosis, and stomatocytosis\(^{14,17–20}\) and Gaucher’s disease\(^{16,21}\).

Based on the literature it is difficult to differentiate if the hypercoaguability is caused by splenectomy from or is due to the underlying hemolytic disorder. Even the risk of PHTN after splenectomy may differ between hemolytic disorders. This suggests that in addition to the loss of splenic filter, the development of PHTN in post-splenectomy patients is likely a slow multifactorial process. In a study by Jaïs et al\(^{11}\) only 4 of 22 patients had a hemolytic disorder, in most of the others, the spleen had been removed for trauma. In another study, of seven patients with unexplained PHTN after splenectomy, 3 patients had splenectomy due to trauma\(^8\). Thus, it is clear that splenectomy by itself is a risk factor for PHTN even in the absence of hematologic disorders. All studies on regarding PHTN have been summarized in Table 3.
MECHANISMS FOR PULMONARY HYPERTENSION POST SPLENECTOMY

Venous thromboembolism and CTEPH

Splenectomy is associated with venous thrombosis in general and in particular, with deep venous thrombosis and non-resolving and recurrent venous thromboembolism[22,23]. Deep venous thrombosis may be complicated by pulmonary embolism. Compared to the general population and appendectomy patients respectively, Thomsen et al[23] found a 19.8-fold (95%CI: 8.8–44.7) and 2.3-fold (95%CI: 1.3–4.1) increased risk of DVT and a 32.6-fold (95%CI: 13.9–76.3) and 3.2-fold (95%CI: 1.8–5.5) higher risk of PE in splenectomized patients within the first 90 d after splenectomy.

One late consequence of non-resolution of venous and pulmonary thromboemboli is CTEPH[24]. This condition is defined by the absence of thrombus resolution after one or more episodes of acute pulmonary embolism causing sustained vascular obstruction and subsequent pulmonary hypertension. In a study by Pengo et al[25] a cumulative incidence of 3% was found for symptomatic chronic thromboembolic pulmonary hypertension in patients with acute pulmonary embolism at 2 year follow up. Autopsies in patients with thalassemia have confirmed microthromboembolism in the pulmonary vasculature[14]. Histologic examination of explanted lungs in patients with unexplained PHTN undergoing lung transplant showed abundant thrombotic lesions in conjunction with medial hypertrophy, plexiform lesions and marked intimal thickening[8]. In a study by Frey et al[26], mass spectral analysis of human pulmonary endarterectomy specimens in CTEPH after splenectomy showed increased anionic phospholipids. These anionic phospholipids inhibit angiogenesis in vitro thereby delaying thrombus resolution[26]. In the same study, thrombi volumes and cross sectional areas were compared in splenectomized and sham-operated mice after inferior vena caval ligation to create stagnant flow venous thrombosis and model human deep vein thrombosis. Splenectomized mice showed larger initial thrombi and delayed thrombus resolution[26]. In the study by Jaïs et al[11] of the 22 patients with CTEPH who had had splenectomy, only eight were suitable for thrombo-endarterectomy. Also, in the same study, only 7 (2.5%) of 276 patients with idiopathic PHTN had splenectomy compared to prevalence of 11.5% of aplenia in patients with unexplained PHTN reported in an earlier study[8]. However, in the study by Hoeper et al[8], splenectomized subjects had prominent thrombotic pulmonary arteriopathy. This raises the possibility of a continuum between CTEPH, thrombotic form of idiopathic PHTN and PAH without thrombosis[27]. Further, it suggests that PHTN after splenectomy occurs mainly through thromboembolic involvement of pulmonary microvasculature. This may occur by two mechanisms; (1) Increased thrombus formation; and (2) Delayed thrombus resolution as discussed below.

Increased thrombus formation

Patients undergoing splenectomy may have significant enrichment of anion phospholipids and this has been proposed to be the key to thrombogencity[26]. In animal studies, platelet-derived micro particles (MP) were significantly increased in the blood of the splenectomised mice[26]. These microparticles can act as pro-coagulants by providing a negative charged surface for the assembly of coagulation proteases thus contributing to thrombus formation[28]. A similar rise in platelet derived MPs was observed in humans after
undergoing splenectomy\textsuperscript{[29]}. Anionic phospholipids of the erythrocyte membrane phosphatidylserine (PS) are localized in the inner membrane leaflet of the cell membrane of red blood cells in normal individuals\textsuperscript{[30]}. The translocation of such phospholipids (e.g., PS) to the outer leaflets of the erythrocyte membrane supports coagulation by acting as cofactors for proteolytic reactions\textsuperscript{[31]}. Kuypers \textit{et al}\textsuperscript{[32]} showed that number of erythrocytes with modified PS expression was 20 times higher after splenectomy. The loss of splenic filtering function allows abnormal red cells to remain in circulation after splenectomy. Thus increased MPs and anionic phospholipids can enhance thrombogenicity, and result in CTEPH.

**Delayed thrombus resolution**

In the mouse models of Frey \textit{et al}\textsuperscript{[26]} the anionic phospholipids PS and phosphatidylycerol (PG) as well as the neutral phospholipid phosphatidylethanolamine (PE) were increased in the later phase of vascular remodeling along with delayed incidence of thrombus resolution. This supports the possibility that cellular effects of these phospholipids may be driving the delay in thrombus resolution. Angiogenesis is a key event in vascular remodeling. It has been demonstrated that non-resolution of the thrombus has been associated with low expression of angiogenesis associated genes. PS may inhibit angiogenesis via brain specific angiogenesis inhibitor 1. This adhesion type G protein coupled receptor binds PS on apoptotic cells. This has shown to inhibit in vivo neovascularization\textsuperscript{[33,34]} that in turn leads to delayed thrombus resolution. While Frey \textit{et al}\textsuperscript{[26]} also demonstrated compromised lymphangiogenesis in splenectomized patients, whether it plays a role in thrombus non-resolution is a subject of further research.

In patients with thalassemia, the high oxidative state of the red blood cells due to iron accumulation in the membrane induces a similar high oxidative state in the platelets, leading to their activation\textsuperscript{[35]}. Furthermore, rheological abnormality of the red blood cells also tends to favor their aggregation\textsuperscript{[36]}. Garozzo \textit{et al}\textsuperscript{[37]} have reported increased adhesion molecules on nucleated red blood cells in patients with thalassemia intermedia and major, which may contribute to the hypercoagulable state. Splenectomized patients with thalassemia have more abnormal red blood cells and precursors thus possibly leading to thrombosis that in turn may lead to elevated pulmonary pressures\textsuperscript{[38]}.

**Thrombocytosis**

Reactive thrombocytosis immediately following splenectomy is due to decreased cell degradation and increases the risk of subsequent venous thromboembolism\textsuperscript{[39,40]}. However, this association is likely due to additional risk factors of severely ill trauma patients included in these studies\textsuperscript{[41]}. No increase in the incidence of thromboembolism was evident directly after splenectomy in another study\textsuperscript{[22]}. Thrombocytosis normally diminishes following splenectomy, however pulmonary hypertension may develop if thrombocytosis persists\textsuperscript{[27]}. Long standing thrombocytosis after splenectomy has been shown in one case to be associated with elevated fibronipeptide A, thromboxane B2 and β-thromboglobulin levels resulting in endothelial damage, local platelet activation and thrombin generation leading to CTEPH. Treatment of the thrombocytosis led to improvement in the clinical condition as well as pulmonary symptoms\textsuperscript{[42]}. In another case treatment with hydroxyurea improved both
vascular and cardiac function in a patient who developed pulmonary hypertension and right heart failure due to thrombocytosis following splenectomy. Singer et al. also showed higher levels of sPECAM-1, which has a role in platelet activation, and adhesion signaling in splenectomized thalassemia intermedia patients. Thus besides thrombocytosis, increased platelet adhesion may contribute to the development of pulmonary vasculopathy.

**Megakaryocytes**

There is strong indirect evidence indicating transmigration of intact megakaryocytes from the bone marrow into the circulation and the release of platelets from these megakaryocytes in the pulmonary capillary bed. These large sized platelet precursors can contribute to distal in situ thrombosis leading to CTEPH after splenectomy. This explains the observation that many patients with CTEPH are not suitable for thromboendarterectomy. In patients with hemolytic anemia and myeloproliferative disorders especially in the setting of splenectomy extramedullary hematopoesis (EMH) occurs, where the megakaryocyte can play a key role. EMH commonly involves the liver and the spleen. However after splenectomy, the lungs can become an alternate site of EMH. Pulmonary EMH has been observed in Gaucher’s disease with the presence of Gaucher’s cells and megakaryocytes in the lungs. Thus the presence of increased megakaryocytes as a result of EMH in pulmonary bed can contribute to PHTN. ‘Pathologic emperipolesis’ is seen in myelofibrosis in which the megakaryocytes cause narrow fibrosis through the release of fibrogenic mediators like vascular endothelial growth factor, platelet derived growth factor (PDGF) and transforming growth factor-β. It has been proposed that megakaryocytes at sites of pulmonary EMH may be responsible for a similar phenomenon which leads to fibrosis of the pulmonary vasculature and PHTN. In sickle cell disease, autosplenectomy can lead to EMH in the lungs and PHTN. While possible mechanisms have been mentioned above, more studies are needed to ascertain the exact role of megakaryocytes in the pathogenesis of PHT after splenectomy.

**Nitric oxide**

In patients with chronic hemolytic disorder, free hemoglobin released from lysed red cells can scavenge nitric oxide, an important pulmonary vasodilator. Elevated cell-free hemoglobin is modestly correlated with mean pulmonary artery pressures and pulmonary vascular resistance in pulmonary arterial hypertension. Splenectomy leads to impaired clearance of senescent red cells especially in patients with hemoglobinopathies. Thus, higher plasma hemoglobin levels and increased scavenging of nitric oxide in splenectomized patients may contribute to pulmonary vasculopathy and the development of PHTN. Nitric oxide also has an inhibitory function on megakaryocytes leading to their apoptosis. Depletion of nitric oxide can lead to increased megakaryocytes in the pulmonary circulation and development of PHTN as mentioned above.

**Endothelin-1**

In the study by Singer et al., endothelin-1 (ET-1), a potent vasoconstrictor produced by vascular endothelial and smooth muscle cells was higher in non-transfused splenectomized thalassemia patients compared to the transfused group. ET-1 is known to cause pulmonary vasospasm and contributes to the development of pulmonary hypertension.
vasoconstriction and thus could play an important role in developing pulmonary vasculopathy after splenectomy. The role of ET-1 is even more crucial, since theoretically ET antagonists can also play a part in the treatment of PHTN in such patients.

**DIAGNOSIS AND MANAGEMENT**

Transthoracic doppler echocardiography in patients with hemoglobinopathies like thalassemia is cost effective and an established screening tool for PHTN. It is also suggested to screen patients with Gaucher’s disease and at high risk for developing pulmonary hypertension\[^{16}\]. Echocardiography may overestimate pulmonary artery pressure. Therefore elevated pulmonary artery systolic pressure on echocardiography should be confirmed by right heart catheterization. Although not all studies on splenectomized patients have used right heart catheterization for the diagnosis of PHTN (Table 3). Splenectomized patients may develop PHTN and hence should be screened for the development of exercise intolerance. However, currently there is no data to support routine screening in patients after splenectomy for non-hematologic disorders for the development of PHTN.

In patients with thalassemia, regular blood transfusions and iron chelation may reduce the need for splenectomy and prevent the development of PHTN\[^{38,44}\]. Proper transfusion therapy likely restores tissue oxygen delivery and suppresses the synthesis of native defective erythrocytes, hence preventing rapid red cell turnover and hypercoagulability. Reduction of platelet counts with hydroxyurea or by the use of an anti-platelet agent has been suggested for the prevention of thrombotic complications in splenectomized non-transfused thalassemia intermedia patients\[^{54}\].

There is a paucity of large randomized, controlled clinical trials demonstrating benefit of currently available PHTN specific therapies in patients with hemolytic disorders as well as in the subset of these patients undergoing splenectomy. According to the WHO classification, patients with PAH are included in group 1, CTEPH in group 3, and those with PHTN due to hemolytic disorders or Gaucher’s disease are included in group 5. Also, patients with PHTN in the setting of splenectomy without other predisposing co-morbidities are included in group 5. WHO treatment guidelines for PHTN for groups 1 and 4 are well defined. However, no recommendations yet exist for the use of PHTN specific therapy in patients with group 5 PHTN. Many patients with PHTN post-splenectomy are treated with vasodilators similar to patients with group 1 PHTN in the absence of overt thromboembolic disease. Therefore, the treatment algorithm for PHTN in post-splenectomy patients remains unclear given the complex interplay of mechanisms discussed previously.

PHTN associated with Gaucher’s disease has been treated with enzyme replacement therapy and anecdotally with adjuvant vasodilator therapies such as prostacyclin, bosentan and/or sildenafil with improvement in clinical and hemodynamic parameters\[^{55}\]. No data specifically addresses PHTN therapy of splenectomized patients with Gaucher’s disease.

Sildenafil, a phosphodiesterase-5 inhibitor was studied in sickle cell disease associated PHTN in the walk-PHaSST trial\[^{56}\]. This was the first multicenter randomized trial of sildenafil in sickle cell disease sponsored by the National Institute of Health. The study was
prematurely terminated due to increased incidence of painful crises in the treatment group\cite{56}.

The efficacy and safety of sildenafil in patients with thalassemia is limited to small studies defining PHTN using Doppler echocardiography\cite{57,58}. Sildenafil has been shown to be safe, improved pulmonary hemodynamics in patients in both studies while in the study by Derchi \textit{et al}\cite{57}, Sildenafil improved exercise capacity.

Both non-selective dual action endothelin receptor antagonists including Bosentan and Macitentan and selective receptor antagonists of endothelin receptor A such as Ambrisentan are approved for treatment of group 1 PHTN. However, a trial with Bosentan in sickle cell disease with pulmonary arterial hypertension was also suspended early because of poor enrollment, and some of the beneficial effects observed were not statistically significant\cite{59}.

Anticoagulation is currently indicated for the treatment of patients with group 1 and 4 PHTN (CTEPH)\cite{60}. However, there is no evidence to support routine use of anticoagulants for the treatment of post splenectomy group 5 PHTN.

Riociguat a soluble guanylate cyclase stimulator approved for CTEPH, and may be considered in patients developing pulmonary hypertension after splenectomy in the setting of pulmonary thromboembolic phenomenon. However, with mechanism of action being related to phosphodiesterase inhibition and lack of safety data in splenectomized patients, routine use in this subgroup of patients is currently not recommended.

**CONCLUSION**

Patients undergoing splenectomy are known to develop pulmonary complications including pneumonia and pleural effusion. However, the development of pulmonary hypertension after splenectomy also needs to be considered. The risk of development of PHTN after splenectomy is currently unknown for any given patient. Nevertheless, this complication does occur after splenectomy likely through a multitude of factors (Figure 1). Further research is required to identify markers or screening tools to predict the development of PHTN in this patient population. Whether therapies approved for specific groups of PHTN would be effective for treatment of patients with PHTN after splenectomy remains to be determined. It is clear that more studies are necessary to guide rational treatment strategies targeting specific mechanisms that lead to PHTN after splenectomy.

It is important for physicians to be vigilant about PHTN as it may develop years or decades after splenectomy. Since PHTN usually manifests with non-specific symptoms, patients should be screened for symptoms such as fatigue, exercise intolerance and dyspnea. Screening for PHTN cannot be underemphasized for post-splenectomy patients with hematologic disorders given increased risk for the development of PHTN in this subgroup. Early recognition is essential to institute interventions that may improve outcome.

**Acknowledgments**

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REFERENCES


Core tip

Pulmonary hypertension is an often underrecognized non-infectious complication after splenectomy. The mechanisms for the development of pulmonary hypertension in this setting are multifactorial and are not clearly elucidated. We attempt to outline and highlight the current evidence behind these proposed mechanisms of post splenectomy related pulmonary hypertension.
Figure 1. Proposed mechanisms for the development of pulmonary vasculopathy after splenectomy
Solid lines represents known mechanisms, Dotted line represents hypothesized mechanisms.
Hb: Hemoglobin; NO: Nitric oxide; EMH: Extra medullary hematopoiesis; MP: Micro-particles; AP: Anionic phospholipids; RBC: Red blood cell; CTEPH: Chronic thromboembolic pulmonary hypertension.
Table 1

Medical complications after splenectomy

<table>
<thead>
<tr>
<th>Early</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower lobe collapse of left lung</td>
<td>Overwhelming infections: bacterial (Streptococcus pneumoniae, Hemophilus influenzae, Staphylococcus aureus, Streptococcus group B, Salmonella species, Escherichia coli and other coliforms, Capnocytophaga canimorsus and rarely Pseudomonas aeruginosa), parasitic (Babesiosis Plasmodium species, Ehrlichiosis)</td>
</tr>
<tr>
<td>Left pleural effusion</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Pulmonary Hypertension</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>Graft vs host disease[61]</td>
</tr>
<tr>
<td>Subphrenic abscess</td>
<td></td>
</tr>
</tbody>
</table>
**Table 2**

World Health Organization's classification of pulmonary hypertension\(^{10}\)

<table>
<thead>
<tr>
<th>Group I - Pulmonary Arterial hypertension (PAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic PAH</td>
</tr>
<tr>
<td>Heritable PAH (BMPR2, ALK1, ENG, SMAD9, CAV1, KCNK3, Unknown)</td>
</tr>
<tr>
<td>Drug and toxin induced</td>
</tr>
<tr>
<td>Associated with (1) Connective tissue disease; (2) HIV infection; (3) Portal hypertension; (4) Congenital heart disease; and (5) Schistosomiasis</td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension of the newborn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group II - Pulmonary hypertension due to left heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular systolic dysfunction</td>
</tr>
<tr>
<td>Left ventricular diastolic dysfunction</td>
</tr>
<tr>
<td>Valvular disease</td>
</tr>
<tr>
<td>Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group III - Pulmonary hypertension due to lung diseases and/or hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
</tr>
<tr>
<td>Sleep-disordered breathing</td>
</tr>
<tr>
<td>Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>Chronic exposure to high altitudes</td>
</tr>
<tr>
<td>Developmental lung disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group IV - Chronic thromboembolic pulmonary hypertension</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Group V - Pulmonary hypertension with unclear multifactorial mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy</td>
</tr>
<tr>
<td>Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleimyomatosis</td>
</tr>
<tr>
<td>Metabolic disorders: glycogen storage disease, Gaucher’s disease, hypothyroidism</td>
</tr>
<tr>
<td>Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension</td>
</tr>
</tbody>
</table>

Adapted from Galiè et al\(^{62}\). BMPR: Bone morphogenetic protein receptor type II; CAV1: Caveolin-1; ENG: Endoglin; HIV: Human immunodeficiency virus.
## Table 3

List of splenectomy and pulmonary hypertension studies

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Patient cohort (n)</th>
<th>Study design</th>
<th>No. of patients with splenectomy</th>
<th>Method of PH diagnosis</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoeper et al(^8)</td>
<td>Unexplained PHTN (61)</td>
<td>Retrospective</td>
<td>7</td>
<td>RHC</td>
<td>3 patients had splenectomy for hereditary spherocytosis and trauma, one patient with ITP</td>
</tr>
<tr>
<td>Jaïs et al(^11)</td>
<td>CTEPH (257)</td>
<td>Retrospective</td>
<td>22 (8.6%)</td>
<td>RHC</td>
<td>15 patients had splenectomy after trauma, 4 with hemolytic disorder</td>
</tr>
<tr>
<td>Jaïs et al(^11)</td>
<td>Idiopathic PHTN (276)</td>
<td>Retrospective</td>
<td>7 (2.5%)</td>
<td>RHC</td>
<td>Lower prevalence of splenectomy in idiopathic PHTN compared to prior study</td>
</tr>
<tr>
<td>Phrommintikul et al(^38)</td>
<td>PHTN in Thalassemia with Hb &lt; 10 g/dL (29)</td>
<td>Retrospective</td>
<td>29 (75.8%)</td>
<td>TTE</td>
<td>Increased prevalence of PHTN with higher nucleated red cells, platelets and transfusion requirement in splenectomised patients than those with intact spleen.</td>
</tr>
<tr>
<td>Elstein et al(^16)</td>
<td>Gaucher’s disease (134), 9 patients had PH</td>
<td>Retrospective</td>
<td>6</td>
<td>TTE</td>
<td>All patients with PHTN had enzyme replacement therapy</td>
</tr>
<tr>
<td>Stewart et al(^35)</td>
<td>Hereditary stomatocytosis after splenectomy (9)</td>
<td>Retrospective</td>
<td>9</td>
<td>2 RHC, 1 on autopsy</td>
<td>3 patients developed CTEPH, one portal hypertension</td>
</tr>
<tr>
<td>Palkar et al(^63)</td>
<td>PHTN after splenectomy (9)</td>
<td>Retrospective</td>
<td>9</td>
<td>RHC</td>
<td>4 patients belonged to group 1, two to group 4 and one each in groups 2, 3 and 5</td>
</tr>
</tbody>
</table>

RHC: Right heart catheterization; TTE: Transthoracic echocardiography; ITP: Immune thrombocytopenic purpura; PHTN: Pulmonary hypertension.