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Assessment of Risk Factors for Postsplenectomy Pulmonary Hypertension

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Abstract

Background Splenectomy has been associated with several long-term complications; pulmonary arterial hypertension has gained special attention. It seems that the absence of a spleen, rather than underlying condition for which the splenectomy was performed, is the primary cause of this condition.

Objectives Assessing the risk factors for development of pulmonary hypertension in different indications of splenectomy

Method Fifty postsplenectomy patients were included and transthoracic echocardiographic study looking for right ventricle size; ejection fraction and pulmonary artery pressure were performed for each patient in addition to complete blood count.

Results The patients' mean age was 32.5±1.8 years. The mean duration after splenectomy was 5.2±0.34 years with a range of 1-10 years**.** Hemoglobinopathies in different types formed 54% (27/50) of these indications, while non hematological indications were reported in 7 cases (14%). Pulmonary arterial hypertension was reported in 22% of patients with mean pressure 30.10±1.18 mmHg. It is positively correlated with right ventricular size. The highest risk of pulmonary arterial hypertension was reported with splenectomy due to hemolytic diseases in comparison with other indication despite persistence of similar risk in non hemolytic indication but of no statistical significance. The more severe degree of anemia has negative correlation with pulmonary arterial hypertension as well as high WBC count unlike thrombocytosis.

Conclusion Whatever the underlying indications of splenectomy, the risk of pulmonary hypertension exists, which may not related only to thrombocytosis but also for anemia and leucocytosis and it needs long duration follow up to be diagnosed.

Key words Splenectomy, pulmonary hypertension.

List of Abbreviation: PAH = pulmonary arterial hypertension, CTEPH = chronic thromboembolic pulmonary hypertension, TTE = Transthoracic echocardiographic, RV = right ventricle, EF = ejection fraction, PAP = pulmonary artery pressure, ITP = immune thrombocytopenic purpura.

Introduction

Splenectomy is not free from variable important long-term complications. Pulmonary arterial hypertension (PAH) is an important vascular complications [1,2] in addition to risk of deep venous thrombosis [3,4], and atherothrombosis [5]. A specific subcategory of PAH is restricted to patients with hemoglobinopathies and/or splenectomy [6].

Idiopathic pulmonary hypertension or chronic thromboembolic pulmonary hypertension (CTEPH) are reported in cases of thalassemia and sickle cell disease [7,8]. The reported prevalence of splenectomy in patients with PAH ranged

from 8.6% to 11.5% compared with 0% to 0.6% in the other groups (patients with other forms of pulmonary disease) [1].

The underlying indication of splenectmoy is one of the factors that play a role in development of postsplenectomy PAH, but it is definitely not the sole factor in this process. The subsequent hyposplenism state is an important issue regardless the presence of ongoing hemolysis or not [1,7,8].

Splenectomy in thalassemic patients will increase the frequency of PAH over the general population [9,10] and similar risk is reported in sickle cell anemia patients (who had auto-spelnectomy) [11].

Many cases were reported as they developing PAH after splenectomy for variable underlying diseases like hereditary stomatocytosis, hereditary spherocytosis, myeloid metaplasia, paroxysmal nocturnal hemoglobinuria, and unstable hemoglobinopathies [12-19].

The aim of this study is to assess the risk factors for development of pulmonary hypertension in different indications of splenectomy.

Methods

A cross sectional study had been conducted on 50 postsplenectomy patients (with different indications and for different durations). They were met at hematology outpatient clinic at Al-Imammain Al-Kadhimain Medical City during their routine follow up over the period between April 2011 and Dec. 2012. For every patient complete history and examination were performed including indication of spelenctomy, duration since spelenctomy, and complications.

Adult patients with sickle cell disease were also included in this study as they have state of hyposplenism secondary to autosplenectomy as it is proven by ultrasonagraphy, but its duration was estimated crudely (since the age of adolescence). In addition to those having splenectomy for combined hemoglobinopathy (these had been referred as other hematologic indications).

Each patient had informed about the enrollment in this study according to declaration of Helsinki. The study was following the local scientific research ethical committee guidelines.

A complete blood count was requested for all patients; in addition to transthoracic echo-cardiographic (TTE) study (using Philips C9) was performed looking for right ventricle (RV) size, ejection fraction (EF) and pulmonary artery pressure (PAP) according to Bernoulli's equation. The normal RV diastolic dimension is11-28 cm^2 and normal EF must be >55%[20]. PAH defined by a mean PAP >25 mm Hg at rest or> 30 mm Hg during exercise [20,21].

Statistical analysis using SPSS program and Microsoft excel program. T test, ANOVA and Spearman's rank correlation study were used considering a *P* value < 0.05 as significant difference.

Results

Total number of patients were 50, [60% were females (30/50))] their ages range from 16-58 years with a mean of (32.5±1.8 years). The mean duration after splenectomy was 5.2±0.34 years with a range of 1-10 years

The most frequent indications for spelenctomy were hemoglobinopathies in different types that form 54% (27/50), while non hematological indications were reported in 7 cases (14%) as demonstrated in (Table 1).

Table 1: Indications of splenectomy

Indications	No. (%)
Different hematological indications	11 (22)
Thalassemia major	10 (20)
Thalassemia intermedia	6 (12)
Immune hemolytic anemia	8 (16)
Immune thrombocytopenic purpura	5 (10)
Hereditary spherocytosis	3 (6)
Surgical indications	7 (14)
Total	50 (100)

Laboratory parameters for patients define that the hemoglobin level varied between 4.00-13.00 g/dl with a mean of 9.93±0.3, the mean platelet count was 480.62±32.4 x 10^3/ml with a range between 150.0 - 886.0 x10^3/ml (Table 2).

Table 2: Hematologic characteristics of the patient group

Laboratory Characteristic	Mean±SE	Range
Hemoglobin (g/dl)	9.93±0.31	4.00-13.00
Platelet x10^3 (/ml)	480.62±32.49	150.00-886.00
WBC x10^3 (/ml)	8.868±0.58	4.00-20.00

Pulmonary hypertension was reported in 22% of patients with mean pressure 30.10±1.18 mmHg through a range between 15-50 mmHg (Table 3).

Table 3: transthoracic Echocardiographic characteristics of the patient group

Echocardiography Characteristic	Mean±SE	Range
RV size (cm^2)	24.68±0.6	14.00-38.00
EF (%)	62.12±0.81	50.00-75.00
PAP pressure (mmHg)	30.10±1.18	15.00-50.00

RV = right ventricle, EF= left ventricle ejection fraction, PAP= pulmonary artery pressure

RV enlargement was documented in 30% of cases (15/50) (Fig. 1).

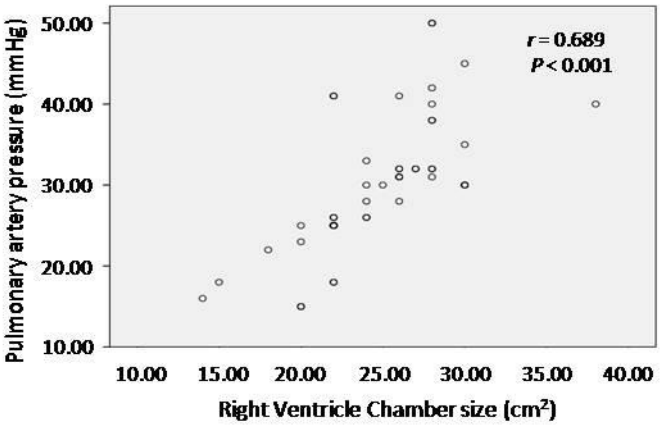

Fig. 1. Distribution of right ventricle size in relation to pulmonary artery pressure

Pulmonary hypertension is positively correlated with RV size in significant value (r = 0.689, P <0.001) but has negative correlation with EF (r = -0.485, P < 0.001).

There are significant differences between genders concerning mean PAP pressure (P = 0.039). Mean PAP pressure in male patients is 33.05±1.98 mmHg while it is 28.13±1.35 mmHg in females with statistically significant difference (P = 0.039)

The highest risk of PAH was reported with splenectomy due to hemolytic diseases (hemoglobinopathies especially thalassemia major and intermedia) in comparison with other indications for splenectomy with statistical significance difference (p = 0.003) (Fig. 2).

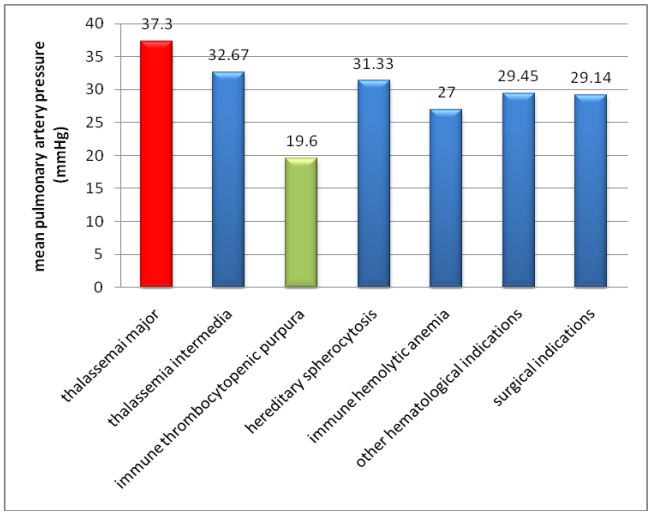

Fig. 2. Comparison of mean PAP among different indications of splenectomy

However; a surgically indicted splenectomy was also associated with risk of pulmonary hypertension but in non significant association (P = 0.065). ITP patients did not show such a risk as their mean PAP is 19.6±1.4 mmHg.

The correlation between PAP and other hematologic parameters were evaluated and It reveals that post splenectomy duration is positively correlated but in non significant value with development of PAH (r = 0.22, P = 0.11) (Fig. 3) and similarly concerning the patient age. While, it is found that the more severe degree of anemia has negative correlation which is of statistical significance with development of PAH (r = -0.314, P = 0.026,) as well as WBC count (r = 0.330, P = 0.019,) unlike thrombocytosis (r = 0.053, P = 0.715).

Discussion

When a patient performed splenectomy, PAH would be a consistent risk consequence

especially in cases of underlying haemolytic anaemia [22].

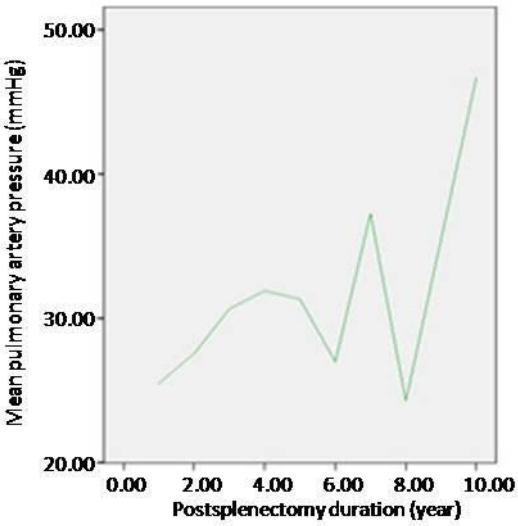

Fig. 3. Relationship of post splenectomy duration and mean pulmonary artery pressure

It is found in over 60% of the patients with thalassaemia [23,24] and while it is reported in patient with sickle cell disease as 32% [25]. The question that is raised, does it follow other indications of splenectomy?

In this study different indications were included, PAH is reported more frequently (22%) than what is reported by Hoeper et al (11.5%) [7]. It can be well understood that this difference may be due to limitation of transthorasic echocardiography in diagnosis of pulmonary hypertension and other variables like the inter operator & intra operator variation [26].

One complicating factor in many of these cases, which is the consideration of splenectomy as a treatment line and therefore it, is difficult to differentiate between the roles of splenectomy per se or the effect of the underlying haemolytic disease in development of PAH.

Hemoglobinpathies, in this study, form the major component of the patients group (54%) which is already known as risk factor for PAH (*P* = 0.003), (a process that may started even before splenectomy) in agreement with report of Aessopos et al [27] who found that 59% of patients with thalassaemia intermedia who had had splenectomy developed thromboembolic pulmonary hypertension and similarly other author conclusion [28].

Despite all these limitations , non hematological indications were forming around 14% of the studied cases which also showed increasing risk of PAH but in non significant manner (*P* = 0.065).

The simplest explanation of the other authors who have studied this problem is that, following splenectomy, there is both thrombocytosis and also increased numbers of damaged circulating red cells which will activate these platelets leading to in situ thrombosis [29,30], but it couldn't be approved in this study as thrombocytosis didn't show any significant correlation with such a risk (*r* = 0.053, *P* = 0.715). In the contrary, the severity of anemia and higher WBC count showed significant negative and positive correlation (*r* = -0.314, *P* = 0.026,) and (*r* =0.330, *P* = 0.019,) respectively.

This may indicate that different factors other than hypercoagulability will play a role like impact of anemia, leucocytosis on blood flow dynamics or endothelial dysfunction [31,32]. Peacock stated that "is not simply one of increased coagulability due to loss of the splenic filter but one of abnormal endothelial surface resulting in *in situ* thrombosis or another factor " [33].

The exact mechanism by which pulmonary hypertension develops after splenectomy remains unclear. The pathophysiological mechanisms have been proposed as": (i) thromboembolic occlusion of the pulmonary vasculature; (ii) an increase in the production of reactive oxygen species; and (iii) the depletion of nitric oxide by free hemoglobin released by damaged red cells leading to pulmonary vasoconstriction" [24].

Some were recognized the presence of megakaryocytes in the lungs, and therefore they postulated their contribution in PAH in these states [24]. Vascular endothelial growth factor, platelet-derived growth factor and transforming growth factor-b will be released there as fiberogenic mediators from these trapped platelets inside capillary beds (regardless the

thrombocyte count in circulation) in a phenomenon called 'pathological emperipolesis' leading to increase in pulmonary artery pressure [34,35].

The mean PAP pressure in those performed splenectomy for other than chronic hematologic disease was 29.14±2.32 mmHg that is consider as evidence for pulmonary hypertension and this was also reported by Jaix et al [1] in his paper at Thorax journal where only four of the 22 patients who developed CTEPH after splenectomy had a haemolytic disorder, and in most of the others the spleen had been removed for trauma which had demonstrated.

Post splenectomy duration is positively correlated but in non significant value with risk of PAH (r = 0.22, P = 0.11) which is noticed by Jaix et al [1] who demonstrated long duration (up to 35yr) required for this complication to be developed that suggest the pulmonary hypertension is a very slow process or that some additional factor developed which resulted in a prothrombotic state, perhaps a change in endothelial function or a change in red cell characteristics. Therefore, any case that needs splenectomy still may have this risk of PAH even for other than hemolytic or hematologic disorders [33]. This consequence may be related erythrocyte membrane alteration and subsequent activation of coagulation cascade due to the loss of spleen filter function [36]. In addition to the fact that in case of trauma, there is an associated thromboembolic complications even if not documented immediately after the surgery [1].

In conclusion, whatever the underlyng indication of splenectomy, the risk of pulmonary hypertension exist, which may not related only to thrombocytosis but also for anemia and leucocytosis and it needs long duration follow up to be excluded. Transthoracic echocardiography can help in this follow up by demonstration of right ventricle size.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Dr. Waseem F. Al Tameemi is the caring physician and hematologist for group of patient; Dr. Maan M. A. Hamid is the surgeon who performed splenectomy and Dr. Haider N. Dawood is the physician who record echocardiography.

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