

Pulmonary Hypertension in Thalassemia: Mechanisms and Treatment

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Synopsis:

Pulmonary hypertension (PHT) is a serious, potentially fatal complication, that develops in a high percentage of patients with thalassemia intermedia (TI) and in a smaller percentage of patients with thalassemia major (TM), resulting in right ventricular deterioration and congestive heart failure. Currently, monitoring of right heart pressure for detection of PHT by echocardiogram is not routinely performed for most TM and TI patients and understanding of this complication is inadequate. Furthermore, intervention for prevention and treatment of established PHT is currently insufficient and not consistent.

Though the pathogenesis of PHT in thalassemia remains unclear, several reports suggest obstruction of pulmonary arteries by thrombotic events, as a hypercoagulable state has been described in this patient population. However, no clinical trials addressing the primary causes, pathophysiology and treatment of this life-threatening complication in thalassemia have been carried out.

We hypothesize that increased platelet activation and hypercoagulability are the prime causes of PHT development. These are likely increased in splenectomized non-transfused TI patients, due to thrombocytosis and excess of damaged RBC, which could trigger thrombosis. This likely results in endothelial injury and proliferation causing obliteration and increased pulmonary vascular pressure. The specific aims of this proposal are as follows:

Aim I: To determine that hypercoagulability is the prime cause for the development of PHT in thalassemia patients, by characterizing markers of coagulation, endothelial damage and inflammation associated with PHT.

Specific indicators of platelet activation, hypercoagulability and endothelial injury will be assessed in thalassemia patients diagnosed with PHT on echocardiography, and compared to the findings in patients without PHT. Clinical parameters including prior splenectomy, level of anemia, degree of iron overload and liver dysfunction will be reviewed for determination of an association with PHT.

Aim II: To institute a pilot intervention trial in patients with PHT to determine if treatment with specific anticoagulant agents will decrease hypercoagulable, inflammatory and endothelial activation markers.

Based on the results in Specific Aim I, patients found to have PHT, will be enrolled in a pilot study aimed to assess the physiological effects of ASA (Aspirin), Warfarin (Coumadin) and the combination of the two. By prospectively treating these patients we will be able to determine if laboratory measures of platelet dysfunction, hypercoagulable, endothelial and inflammatory markers improve with these treatment agents.

This study will provide scientific foundation for the pathogenesis of PHT and identify specific markers linked to its progression; it will instigate a pilot interventional trial that will employ the markers predicting PHT, as characterized in the first part of the study. This data will be crucial in supporting the need for further clinical trials.