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Pulmonary Hypertension in Sickle Cell Disease: Pathophysiology and Management

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Introduction

Approximately 10% of adult sickle cell disease (SCD) patients experience pulmonary hypertension, particularly those who have the homozygous genotype. Although right-heart catheterization is necessary for a conclusive diagnosis, a rise in pulmonary artery systolic pressure, which may be measured noninvasively by echocardiography, aids in the identification of SCD patients at risk for pulmonary hypertension. Precapillary pulmonary hypertension, with potential etiologies of (1) a nitric oxide deficiency state and vasculopathy as a result of intravascular hemolysis, (2) chronic pulmonary thromboembolism, or (3) upregulated hypoxic responses secondary to anaemia, low O2 saturation, and microvascular obstruction, affects about half of patients with SCD-related pulmonary hypertension. The remaining individuals have postcapillary pulmonary hypertension brought on by left ventricular dysfunction. The risk of death is significantly higher in SCD patients with pulmonary hypertension than in individuals without pulmonary hypertension, despite the fact that their pulmonary artery pressure is only mildly increased. The American Thoracic Society just released guidelines for the identification and treatment of pulmonary hypertension caused by SCD [1]. Adults with sickle-related pulmonary hypertension are managed with anticoagulation for those who have thromboembolism, oxygen therapy for those who have low oxygen saturation, treatment of left ventricular failure in those who have postcapillary pulmonary hypertension and hydroxyurea or transfusions to increase haemoglobin concentration, decrease hemolysis, and stop vaso-occlusive events that lead to additional increases in pulmonary pressure. In SCD patients with precapillary pulmonary hypertension, medications to reduce pulmonary pressure have not been discovered through randomised trials. Patients with hemodynamic of pulmonary arterial hypertension should be directed to specialised facilities and given consideration for treatments that have been shown successful in treating other kinds of pulmonary arterial hypertension [2]. Some of these therapies are claimed to reduce pulmonary hypertension brought on by SCD. Sickle cell disease (SCD) is brought on by compound heterozygosity, such as haemoglobin SCD and haemoglobin S-thalassemia, or by homozygosity for the Glu6Val mutation in HBB (sickle cell anaemia; haemoglobin SS). This mutation causes the creation of haemoglobin with an aberrant structural makeup (haemoglobin S). The primary cause of the negative effects of hemolysis, vaso-occlusion, chronic inflammation, anaemia, and elevation of hypoxic responses is haemoglobin S polymerization. Since pulmonary hypertension impacts the pathogenesis, classification, and prognosis of SCD, it is important to take into account both the prevalence of pulmonary hypertension in SCD and the larger picture of pulmonary hypertension in patients without SCD.

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Description

The World Symposium on Pulmonary Hypertension defines pulmonary hypertension as mean pulmonary artery pressure 25 mm Hg at rest as assessed by right cardiac catheterization. The therapeutic significance of people with mean pulmonary artery pressure between 21 and 24 mm Hg is being debated. The maximum limit of normal for mean pulmonary artery pressure is 20 mm Hg. This range may identify individuals with decreased exercise capacity and poor results. Some authorities regard this range to describe borderline pulmonary hypertension. Pulmonary hypertension is clinically broken down into five major groups [1]. The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society includes pulmonary arterial hypertension associated with SCD and other haemolytic anaemia's in Group 1 of its guidelines, which were released in 2009. The decision to shift pulmonary hypertension with unknown or numerous etiologies, including SCD, from Group 1 to Group 5 was taken during the Fifth World Symposium on Pulmonary Hypertension in 2013. Pneumatic arterial hypertension in Group 1 affects the intima, medium, and adventitia of the pulmonary arteriolar wall pathologically. Medial hypertrophy is caused by an increase in the quantity and size of smooth muscle cells in the vessel wall media. Intimal proliferation results from the movement of smooth muscle cells from the media to the layer of endothelial cells that typically lines the artery lumen. Endothelial cell growth and an interstitial layer of myogenic cells make up plexiform lesions in the artery lumen. The adventitia, a layer that acts as a resource for the healing of vessel damage, thickens as a result of the expansion of cells around the media, including fibroblasts, progenitor cells, macrophages, and other immune cells [2]. The other types of pulmonary hypertension can also cause changes that are similar to those seen in pulmonary arterial hypertension, though to a lesser or greater extent. The pulmonary veins and capillaries are also swollen in Group 2 pulmonary hypertension brought on by left heart dysfunction. Organized thrombi replace the intima of the proximal or distal elastic pulmonary arteries in Group 4 chronic thromboembolic pulmonary hypertension (CTEPH), adhere to the medial layer, and result in varying degrees of lumen stenosis or total blockage. Collateral arteries from the systemic circulation may grow to reperfuse completely occluded locations, and changes resembling pulmonary arterial hypertension may manifest in no occluded regions. When it comes to hemodynamic, pulmonary hypertension is further divided into precapillary pulmonary hypertension and postcapillary pulmonary hypertension depending on whether the right heart catheterization measured the pulmonary capillary wedge pressure (PCWP) or the left ventricular end-diastolic pressure (LVEDP) at a value less than or equal to 15 mm Hg [3]. Practically speaking, the hemodynamic grouping of postcapillary pulmonary hypertension and the clinical grouping of Group 2 pulmonary hypertension both pertain to the same condition.

Generally speaking, a reliable estimation of systolic pulmonary artery pressure is thought to be the tricuspid regurgitation velocity (TRV) obtained during echocardiography in conjunction with predicted right atrial pressure. The average pulmonary arterial pressure is thought to be 25 mm Hg, while pulmonary hypertension is defined as a mean pulmonary arterial pressure 2.5 m/sec. However, elevation of TRV and estimated systolic pulmonary artery pressure do not accurately identify people with pulmonary hypertension [4]. Instead, an increased TRV can be used to identify patients who need a right cardiac catheterization for a more thorough examination. If the TRV is less than 2.8 m/sec and there are no additional echocardiographic alterations that could

indicate pulmonary hypertension, such as right-sided chamber expansion or right ventricular systolic dysfunction, pulmonary hypertension is regarded as unlikely. The diagnosis is seen as being likely if the TRV is greater than 3.4 m/sec and plausible if it is between 2.9 and 3.4 m/sec.

About 30% of persons with haemoglobin SS and 10% to 25% of adults with haemoglobin SC had elevated systolic pulmonary artery pressure as determined by TRV during Doppler echocardiography. In addition, activity causes unusually high PA systolic pressure in more than half of persons with haemoglobin SS who do not have higher TRV at rest. Adults with haemoglobin SS have lower exercise tolerance and lower survival when there is even a slight rise in systolic pulmonary pressure. Additionally, 10% to 15% of children with SCD exhibit higher systolic pulmonary artery pressure; although the implications for survival are unknown, this observation seems to be associated with a decreased capacity for activity. Adults with elevated systolic pulmonary artery pressure at right heart catheterization that are found to not have pulmonary hypertension have similar survival to SCD patients without elevated TRV, indicating that the elevated mortality with high TRV is primarily driven by the subset of patients who do have pulmonary hypertension. Despite having relatively modest mean pulmonary artery pressures, a striking clinical hallmark of sickle-related pulmonary hypertension is its high mortality. In contrast to other patients with pulmonary arterial hypertension (such as idiopathic and scleroderma-associated patients), where morbidity and mortality are typically associated with mean pulmonary arterial pressures in the range of 50 to 60 mm Hg, these phenomena are observed in patients with SCD with mean pulmonary pressures in the range of 30 to 40 mm Hg, with mild elevations in pulmonary vascular resistance [5].

Conclusion

The cardiac output is negatively correlated with mortality in non-SCD patients with pulmonary arterial hypertension. The cardiac output is significantly higher in SCD patients with or without pulmonary hypertension than it is in nonanemic people. According to this theory, people with SCD-related pulmonary hypertension might be predicted to live longer than those with pulmonary arterial hypertension who do not have SCD, but this is not the case. Any level of pulmonary hypertension seems to be poorly tolerated and causes appreciable morbidity and mortality in patients with anaemia near the limits of cardiac output compensation [6]. Additionally, SCD patients with pulmonary hypertension experience "acute on chronic" pulmonary hypertension as a result of recurrent SCD consequences such pain crises81 and particularly acute chest syndrome, which decreases their chance of surviving these sickle-related problems. The National Heart, Lung, and Blood Institute's Expert Panel concluded in 2014 that "there is insufficient evidence to make a recommendation supporting regular screening with Doppler echocardiography for pulmonary hypertension because studies demonstrating benefit of treating pulmonary hypertension are not available." In contrast, the American Thoracic Society's Ad Hoc Committee on Pulmonary Hypertension of Sickle Cell Disease reported in the same year that "committee members routinely perform risk stratification on their patients with SCD by measuring the TRV via Doppler echocardiography," and recommended screening every 1 to 3 years. The Ad Hoc Committee of the American Thoracic Society's goal was to establish accepted methods for treating high-risk SCD in patients with pulmonary hypertension. The Ad Hoc Committee's proposed guidelines for evaluating SCD patients for pulmonary hypertension are summarised. Even mild anaemia has a negative impact on survival in patients with non-SCD pulmonary arterial hypertension. Anaemia was associated with higher mortality despite increasing cardiac output, a hemodynamic feature that predicts longer survival. Although, as previously discussed, the degree of elevation in mean pulmonary artery pressure is modest; it appears possible that SCD patients' anaemia could contribute to the high mortality of SCD patients with pulmonary hypertension. Case reports suggest that exchange blood transfusion, an intervention that improves anaemia, is beneficial to SCD patients with pulmonary hypertension. To address the high mortality rate in SCD patients with severe pulmonary hypertension, randomised, controlled trials of exchange transfusions are required. Though such trials are still lacking, it appears likely that in the United States, the median survival of adult SCD patients with pulmonary hypertension has improved in the last decade in association with echocardiographic screening and better care of patients with this complication. The current median survival of SCD pulmonary hypertension patients is more than 6 years16, which is more than three times longer than the 2.1 years reported for a corresponding group of SCD pulmonary hypertension patients studied more than a decade ago. The similarity in their pulmonary hemodynamic (mean pulmonary artery pressure of 36 mm Hg in both series) supports the conclusion that the longer survival is not due to more severe patients studied in the 2003 report. It is also unlikely that the longer SCD pulmonary hypertension patient survival is simply a result of advances in general SCD medical care: survival was similar in both studies for patients whose right heart catheterization results did not show pulmonary hypertension [7]. It appears possible that routine ECHO screening of SCD adults over the past ten years has identified a group of patients with a higher risk of passing away, and that their referral to SCD pulmonary hypertension-specialized centres has allowed interventions like intensification of SCD-specific treatment and/or in some cases pulmonary arterial hypertension-specific treatment, which may have lowered their mortality. This positive trend should encourage the development of more controlled studies involving innovative pharmacological treatments and transfusion therapy to lower pulmonary hypertension-related mortality in SCD.

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