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Letter to the Editor: Response to “Updated Clinical Classification of Pulmonary Hypertension”

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We read with interest the “Updated Clinical Classification of Pulmonary Hypertension” by Simonneau et al. in the December 24, 2013 issue of the JACC (1). We are concerned that while systemic sclerosis, portal hypertension, schistosomiasis, and chronic hemolysis result in PH that spans several diagnostic groups, the rules for subgroup inclusion into Group I have not been consistently applied. On behalf of the American Thoracic Society-sponsored soon-to-be-published Clinical Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension (PH) in Sickle Cell Disease (SCD) Committee (Klings ES, et al. AJRCCM 2014 in press), we would like to clarify several points. PH associated with chronic hemolysis has been moved to Group V in the 2013 classification based upon 1) different histopathology and lower pulmonary vascular resistance (PVR) compared with other pulmonary arterial hypertension (PAH) subgroups; and 2) no proven response to PAH-specific medications. While we agree that SCD-PH is multifactorial, the hemodynamics of precapillary PH in SCD need to be clarified. We have defined precapillary SCD-PH like other PAH subgroups: mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg with mean pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure ≤ 15 mm Hg, plus increased PVR. However, what constitutes increased PVR in SCD differs from other PAH subgroups. Anemia-induced elevation of cardiac output and reduction in blood viscosity results in a lower premonitory PVR (2). In idiopathic PAH, increased PVR is defined as ≥ 240 dynes \cdot sec \cdot cm $^{-5}$, 2 standard deviations above the premonitory PVR of ≤ 80 -120 dynes \cdot sec \cdot cm $^{-5}$. Three hemodynamic studies (3-5) have demonstrated that SCD adults without PH had a mean cardiac output of 8-9 L/min with a PVR of 72 - 74 ± 25 - 38 dynes \cdot sec \cdot cm $^{-5}$. In the absence of a consensus definition of elevated PVR in SCD, experts consider values that are 2-3 standard deviations above normal (i.e., ≥ 160 dynes \cdot sec \cdot cm $^{-5}$) to be significant.

We agree that the literature evaluating PAH therapy in SCD-PH is limited. However, we also believe that the 3 clinical trials conducted in these patients are insufficient to determine whether SCD patients with precapillary PH should receive PAH therapy. These trials collectively enrolled only 14 patients with precapillary PH (fewer than half of whom received vasodilators) resulting in imprecisely estimated effects (6,7). There are 4 case series in which SCD patients with precapillary PH were treated with bosentan, sildenafil, and/or epoprostenol. Vasodilator therapy led to an increase in six-minute walk distance 41 to 144 m above baseline (8-10) with improvements in mPAP, PVR, and cardiac index (10). Based upon these studies combined with our clinical experience, we weakly recommended a trial of either an endothelin receptor antagonist or a prostacyclin analog for select SCD patients with symptomatic precapillary PH. We are concerned that the 2013 classification will limit access for these patients to clinically beneficial PAH-specific medications.

The reclassification of SCD-PH as Group IV, Group I, and now as Group V reflects the imprecise nature of the classification. It stresses the need to define PH subgroups so that all patients may benefit from the available treatment options.

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