Author's Reply

We appreciate the input from Rodrigo et al.,[1] regarding circulating endothelial progenitor cells (EPCs) in patients with sickle cell disease (SCD). Pulmonary arterial hypertension (PAH) is a major complication of SCD with high mortality.[2] Since the discovery of EPCs by Asahara et al.,[3] in 1997; interest has been impelled by studies showing that the number and function of these cells correlate with cardiovascular risk factors, endothelial impairment, and may also predict clinical outcome.[4,5] Since endothelial impairment is hallmark of PAH,[6] several studies have implicated EPCs in pathogenesis of PAH.[7]

In our study,[8] for the first time we reported that there are different subpopulations of EPCs in patients with SCD. These subpopulations of EPCs are differentially affected in patients with SCD related PAH and their relative deficiency may contribute to the pulmonary vascular pathology. In our study statistical analyses were performed using Wilcoxon t-test and Spearman's correlation. Several clinical parameters were compared and multivariate regression analysis was applied to determine independent relations of all clinical variables. Results were consistent on repeat analysis and artifact is unlikely.

In the study by Rodrigo et al., the findings of lower number of EPCs in patients with SCD and its association with elevated tricuspid regurgitant jet velocity (TRV) are actually consistent with the results of our study; however there are some fundamental differences between the two studies. In our study, we used right heart catheterization as selection criteria for PAH which is considered as gold standard, while in study by Rodrigo et al., the patients were selected based on high vascular cell adhesion molecule 1 (VCAM1) expression level. VCAM1 is a cell surface sialoglycoprotein highly expressed on endothelial cells following cytokine stimulation. Although VCAM1 is implicated in adhesion of white blood cells (WBCs) to vascular endothelium, its expression is primarily correlated with increase adhesion of red blood cells (RBCs) to vascular endothelial cells in SCD patients[9] and should not be the selection criteria for EPCs studies. Also, constitutive expression of VCAM1 was shown on the bone marrow stromal cells with the possible function of hematopoietic stem cell mobilization and not EPCs.[10] Similarly, TRV alone is nonspecific for the diagnosis of PAH. In addition, we are not sure of the markers used for identification of cells as EPCs by Rodrigo et al., as the term EPC has been widely used and comprises heterogeneous population of mononuclear cells. Furthermore, use of fibronectin cell culture assay (vs our flow cytometry dependent selection) is likely associated with contamination with other type of cells. Activated T lymphocytes contamination was noted in their gene expression analysis; therefore, caution should be used while interpreting these results.

In conclusion it is difficult to compare these observations with our flow cytometry based EPC analysis. Regardless of the different parameters used in these two different studies, EPCs seem to be a fascinating tool that can serve as a suitable prognostic and therapeutic target in patients with SCD related PAH. More studies are required in this area.

Raj Wadgaonkar, and Fatima Anjum

Dept. of Pulmonary Medicine,
SUNY Downstate Medical Center, Brooklyn, NY 11203,
United States
Email: raj.wadgaonkar@downstate.edu

REFERENCES

1. Rodrigo M, Mendelsohn L, Bereal-Williams C, Hunter L, Dalby CK, McGowan V 2nd, et al. Circulating endothelial progenitor cells in adults with sickle cell disease. Pulm Circ 2013;3:448-9.
2. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: Cardiac catheterization results and survival. Blood 2003;101:1257-61.
3. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science 1997;275:964-7.
4. Hill JM, Zalos G, Halcox JP, Schenke WH, Waclawiw MA, Quyyumi AA, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med 2003;348:593-600.
5. Vasa M, Fichtlscherer S, Aicher A, Adler K, Urbich C, Martin H, et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. Circ Res 2001;89:E1-7.
6. Budhiraja R, Tuder RM, Hassoun PM. Endothelial dysfunction in pulmonary hypertension. Circulation 2004;109:159-65.
7. Junhui Z, Xingxiang W, Guosheng F, Yunpeng S, Furong Z, Junzhu C. Reduced number and activity of circulating endothelial progenitor cells in patients with idiopathic pulmonary arterial hypertension. Respir Med 2008;102:1073-9.
8. Anjum F, Lazar J, Zein J, Jamaleddine G, Demetis S, Wadgaonkar R. Characterization of altered patterns of endothelial progenitor cells in sickle cell disease related pulmonary arterial hypertension. Pulm Circ 2012;2:54-60.
9. Setty BN, Stuart MJ, Dampier C, Brodecki D, Allen JL Hypoxaemia in sickle cell disease: Biomarker modulation and relevance to pathophysiology. Lancet 2003;362:1450-5.
10. Taylor JG 6th, Tang DC, Savage SA, Leitman SF, Heller SI, Serjeant GR, et al. Variants in the VCAM1 gene and risk for symptomatic stroke in sickle cell disease. Blood 2002;100:4303-9.

Access this article online

Quick Response Code:

Website: www.pulmonarycirculation.org