Vasoreactivity in PAH

Section Editors:
Jonathan D. Rich, MD
Northwestern University
Feinberg School of Medicine
Chicago, Illinois

Oksana A. Shlobin, MD
Inova Health System
Falls Church, Virginia

In this edition of *Advances*, new section editors Jonathan Rich, MD, and Oksana Shlobin, MD, review the findings from 3 recent investigations than lend support to the argument that vasoreactive PAH is a distinct phenotype and probably a distinct genotype of PAH. Watch for their reports on emerging research with implications for clinicians in future issues of *Advances*.

Within the category of idiopathic pulmonary arterial hypertension (IPAH) is a subset of patients who express pulmonary vasoreactivity when challenged at the time of diagnosis with one of several drugs that produce acute vasodilatation. This has become an established hemodynamic marker of response, and is currently advocated in every clinical practice guideline for patients with pulmonary arterial hypertension (PAH).[1,2] While vasoreactivity is a continuum rather than an all or none phenomenon, the most commonly used clinical criteria today is a fall in mean pulmonary artery pressure (PAP) of at least 10 mm Hg to a level below 40 mm Hg, with no change or an increase in cardiac output. This definition came from the 1998 World Health Organization (WHO)-sponsored symposium on primary pulmonary hypertension, but was an arbitrary definition and not based on scientific data.[3] The long-term effects of treating vasoreactive PAH patients with relatively high doses of calcium channel blockers (CCBs) has resulted in markedly enhanced survival (>20 years for many), with a return to normal or near normal exercise tolerance.[4] The biologic basis of this subgroup, however, remains uncertain.

In nearly all reported pathologic case series of PAH, varying degrees of medial hypertrophy exist in the pulmonary vasculature, which is interpreted as an expression of underlying vasoconstriction.[5] The wide spectrum of responsiveness to vasodilator challenge was thought to be a reflection of the chronicity and the underlying severity of the disease. Although it has not been possible to relate the presence of vasoreactivity specifically to the vascular changes noted on histology, one study reported a qualitative relationship between the patients with more advanced lesions and a reduced likelihood to respond to acute vasodilator testing.[6] This study did not clarify whether the presence of vasoreactivity represents a different stage of the disease or a different disease altogether. While it has long been debated whether the favorable response to acute vasodilator challenge and treatment with CCBs identifies a unique subset of patients with IPAH or different stages of IPAH, 3 recent investigations lend additional strong support to the argument that vasoreactive PAH is a distinct phenotype and probably a distinct genotype of PAH.

Langleben et al[7] determined the status of the functional capillary surface area (FCSA) in the lung in patients with IPAH at diagnosis. In the vasoreactive patients, baseline FCSA was normal and increased dramatically during vasodilator challenge. The data support that the increased cardiac output (CO) occurred by true microvascular recruitment and not via distention. The nonreactive IPAH patients had reduced FCSA at baseline, and acute vasodilator testing did not expose more FCSA despite an average 36% increase in CO. This suggests the nonreactive IPAH patients were unable to open occluded arterioles and recruit more downstream capillaries, but rather the increased blood flow simply passes through the remaining patent and already maximally recruited vascular tree.

Next, Halliday et al[8] retrospectively evaluated 155 consecutive PAH patients referred for right heart catheterization and acute vasodilator testing. Patients were stratified into 3 categories based on response to acute vasodilator challenge:

a. Classic response: Reduction in mean PAP by >10 mm Hg to a value >40 mm Hg
b. Nonclassic response: Reduction in mean PAP >10 mm Hg but to a value >40 mm Hg
c. Nonresponse: Reduction in mean PAP <10 mm Hg

Consistent with previous reports, 13% of patients demonstrated a classic response to vasoreactivity testing. In the remainder, 8% had a nonclassic response, and 79% of patients were nonresponders. Among the key findings in this study were:

a. Those with a classic response to vasodilator testing had an impressive long-term survival benefit consistent with the original description of this phenomenon,[9] whereas there was no survival benefit in those with a nonclassic response compared to nonresponders.
b. Among those with a classic response, 40% had connective tissue disease, yet only IPAH patients demonstrated a survival benefit.

Finally, Hemnes et al[10] studied the genetic basis of this population using RNA expression patterns in peripheral blood. Microarrays of cultured lymphocytes from vasoreactive and non-vasoreactive PAH patients were performed with quantitative polymerase chain reaction (PCR) done on peripheral blood, and a decision tree was then developed to identify vasoreactive patients. Broad differences in gene expression patterns on microarray analysis were seen including cell-cell adhesion factors, cytoskeletal genes, and rho/GTPase genes. Ten decision trees were built using expression levels of 2 genes as the primary genes: DSG2, (a desmosomal cadherin involved in Wnt/β-catenin signaling), and RHOQ (which encodes a cytoskeletal protein involved in insulin-mediated signaling). These trees correctly identified all vasoreactive patients in a separate validation cohort. This is the first genotype correlation for a phenotypic subset in the history of pulmonary hypertension research.

These important recent contributions to the PAH field provide a compelling argument that vasoreactive PAH is a distinct phenotype and likely a distinct genotype of disease. It also serves as an important reminder to all clinicians and reinforces the published guidelines of the critical importance of acute vasodilator testing in all patients with IPAH to identify this unique subset of patients in whom treatment with CCBs is likely to result in a markedly improved outcome.

References

1. Galiè N, Hoeper MM, Humbert M, et al; ESC Committee for Practice Guidelines. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009; 30(20):2493-2537.
2. McLaughlin VV, Archer SL, Badesch DB, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society, Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol.* 2009;53(17):1573-1619.
3. Primary Pulmonary Hypertension Executive Summary from the World Symposium. In: Rich S, Rubin LJ, Abenhaim L, eds. Evian, France, 1998.
4. Rich S. The current treatment of pulmonary arterial hypertension: time to redefine success. *Chest*. 2006;130(4):1198-1202.
5. Pietra GG, Edwards WD, Kay JM, et al. Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. *Circulation*. 1989; 80(5):1198-1206.
6. Palevsky HI, Schloo BL, Pietra GG, et al. Primary pulmonary hypertension. Vascular structure, morphometry, and responsiveness to vasodilator agents. *Circulation*. 1989;80(5):1207-1221.
7. Langleben D, Orfanos SE, Giovinazzo M, et al. Acute vasodilator responsiveness and microvascular recruitment in idiopathic pulmonary arterial hypertension. *Ann Intern Med.* 2015;162(2): 154-156.
8. Halliday SJ, Hemnes AR, Robbins IM, et al. Prognostic value of acute vasodilator response in pulmonary arterial hypertension: Beyond the "classic" responders. *J Heart Lung Transplant.* 2015; 34(3):312-318.
9. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med.* 1992;327(2):76-81.
10. Hemnes AR, Trammell AW, Archer SL, et al. Peripheral blood signature of vasodilator-responsive pulmonary arterial hypertension. *Circulation*. 2015;131(4):401-409.