Article Reviews

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Summaries and commentaries from the section editors present a clinical context for practitioners' application of recently published research relevant to care of patients with pulmonary hypertension. This issue's reviews were prepared by Dr Bull.

Shah AA, Wigley FM, Hummers LK. Telangiectases in scleroderma: a potential clinical marker of pulmonary arterial hypertension. *J Rheumatol*. 2010;37(1):98-104.

Telangiectases are a well recognized physical finding of scleroderma. In this article, Shah and colleagues examined whether increasing numbers of telangiectases were associated with pulmonary hypertension. They counted the number of telangiectases from 11 defined body parts of 147 patients with scleroderma. The patients were assigned a score of 0 if there were no telangiectases, 1 if there were fewer then 10, and 2 if there were 10 or more lesions. A statistically significant positive correlation was discovered between the telangiectasia score and the degree of pulmonary hypertension estimated by RVSP (r=0.21, *P*=0.001), which remained significant on multivariant analysis. RVSP increased by 10.9 mm Hg for every 10-point incremental increase in the telangiectasia score. They also noted that the number of telangiectases increased linearly with the age of the patient, and that serum endoglin levels correlated positively with increasing telangiectasia scores in a subset of patients. There was a negative correlation between the score and forced vital capacity and diffusing capacity of the lung for carbon monoxide.

The authors speculate the development of telangiectases is a marker of developing vascular anomalies, including changes in the pulmonary vasculature. A criticism of the study is the noninvasive (echocardiographic) assessment of pulmonary artery pressures as a primary end point. However, the findings were confirmed in a smaller cohort of pulmonary arterial hypertension patients who underwent right heart catheterization. The correlation did not reach statistical significance in the catheterized patients diagnosed with pulmonary venous hypertension. The authors postulate that the quantification of these cutaneous lesions could serve as a readily accessible biomarker of pulmonary vascular disease in patients with scleroderma. Whether or not a worsening telangiectasia score can be used to predict the development of pulmonary hypertension requires further investigation.

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Smith TG, Talbot NP, Privat C, et al. Effects of iron supplementation and depletion on hypoxic pulmonary hypertension: two randomized controlled trials. *JAMA*. 2009;302(13):1444-1450.

The authors report their findings from 2 small, randomized, placebo-controlled protocols performed in Peru. In the first protocol, 22 healthy individuals living at sea level (Lima, Peru) were brought to high altitude (Cerro de Pasco, Peru), elevation 4340 meters (14,238 feet). Their pulmonary arterial systolic pressures (PASPs) were documented by echocardiography with a mean increase of 14 mm Hg, from a baseline value of 24 mm Hg to 39 mm Hg when at altitude. The patients were then given an infusion of Fe (III)-hydroxide sucrose (200 mg in 100 mL). Their measurements of PASP by echocardiography were repeated with noted improvement in the PASP to a mean of 31 mm Hg.

In the second trial, 11 patients who lived chronically at altitude and who had previously been diagnosed with chronic mountain sickness (excessive erythrocytosis Hgb>21 g/dL, hypoxia, and absence of other chronic pulmonary disease) had baseline measurements of PASP recorded and then underwent phlebotomy (isovolemic venesection) of 500 mL daily for 4 consecutive days. Measurements of PASP were repeated at Days 5, 12, and 19. There was a statistically significant increase in PASP following the venesection (mean 4 mm Hg acutely and approximately 10 mm Hg at the end of the study). These patients were divided into a treatment arm and a placebo arm, with the treatment arm receiving intravenous infusions of Fe (III)-hydroxide sucrose (2 infusions of 200 mg separated by 2 days). The Fe infusion and placebo patients were then crossed over on Day 25. Hemodynamic measurements were then again made by echocardiography. In patients with chronic mountain sickness, the IV Fe (III) was not noted to decrease PASP.

Criticisms of the study include the small number of patients and the noninvasive nature of the hemodynamic measurements. One must also question the generalizability of the findings to all hypoxic pulmonary hypertension patients from this narrow patient population. It is important to note that these are not pulmonary arterial hypertension (WHO class I) patients. It is unclear from this study what the mechanism of pulmonary arterial pressure change from iron depletion and supplementation was. However, the study design was predicated on previous interesting observations from the authors and others regarding the interaction of iron (Fe II) as a cofactor in the degradation of hypoxia-inducible facto.[1-3]

Overall, if these observations prove to be correct, there is the potential for great clinical significance, both in terms of targeting novel therapies as well as redirecting attention toward the importance of management of anemia, polycythemia, iron overload, and iron depletion states in patients with pulmonary hypertension.

References

1. Wang GL, Semenza GL. Desferrioxamine induces erythropoietin gene expression and hypoxia-inducible factor 1 DNA-binding activity: implications for models of hypoxia signal transduction. *Blood*. 1993;82:3610-3615.
2. Knowles HJ, Raval RR, Harris AL, Ratcliffe PJ. Effect of ascorbate on the activity of hypoxia-inducible factor in cancer cells. *Cancer Res*.

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18. Creed F, Dickens C. Depression in the medically ill. In: Steptoe A, ed. *Depression and Physical Illness*. 1st ed. Cambridge, UK: Cambridge University Press; 2007:3-19.
19. Rumsfeld JS, Havranek E, Masoudi FA, et al; Cardiovascular Outcomes Research Consortium. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. *J Am Coll Cardiol.* 2003;42(10):1811-1817.
20. Rumsfeld JS, Magid DJ, Plonomdon ME, et al. History of depression, angina, and quality of life after acute coronary syndromes. *Am Heart J.* 2003;145(3):493-499.
21. Ziegelstein RC. Depression in patients recovering from a myocardial infarction. *JAMA.* 2001;286(13):1621-1627.
22. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation.* 1999;99(16):2192-2217.
23. Hansen MS, Fink P, Frydenberg M, Oxhøj M, Søndergaard L, Munk-Jørgensen P. Mental disorders among internal medical inpatients: prevalence, detection, and treatment status. *J Psychosom Res.* 2001;50(4):199-204.
24. Moser DK. Psychosocial factors and their association with clinical outcomes in patients with heart failure: why clinicians do not seem to care. *Eur J Cardiovasc Nurs.* 2002;1(3):183-188.
25. Feinstein RE, Blumenfield M, Orlowski B, Frishman WH, Ovanessian S. A national survey of cardiovascular physicians' beliefs and clinical care practices when diagnosing and treating depression in patients with cardiovascular disease. *Cardiol Rev.* 2006;14(4):164-169.
26. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord.* 2009;114(1-3):163-173.
27. Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. *Psychiatr Clin North Am.* 2002;25(4):685-698.
28. Dunlop BW, Self RL. Exercise for depression: efficacy, safety and clinical trial implications. *Psychopharmacol Bull.* 2008;41(4):65-75.
29. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation.* 2006;114(14):1482-1489.
30. McCollister DH, Beutz M, McLaughlin VV, et al. Depressive Symptoms in Pulmonary Arterial Hypertension: Prevalence and Impact on Functional Status. *Am J Respir Crit Care Med.* 2009;179:A2663.
31. Kawut SM, Horn EM, Berekashvili KK, et al. Selective serotonin reuptake inhibitor use and outcomes in pulmonary arterial hypertension. *Pulm Pharmacol Ther.* 2006;19(5):370-374.
32. Shah SJ, Gomberg-Maitland M, Thenappan T, Rich S. Selective serotonin reuptake inhibitors and the incidence and outcome of pulmonary hypertension. *Chest.* 2009;136(3):694-700. ■

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2003;63:1764-1768.
3. Smith TG, Balanos GM, Croft QP, Talbot NP, Dorrington KL, Ratcliffe PJ, Robbins PA. The increase in pulmonary arterial pressure caused by hypoxia depends on iron status. *J Physiol.* 2008;586:5999-6005.

Toshner M, Voswinckel R, Southwood M, et al. Evidence of dysfunction of endothelial progenitors in pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2009;180(8):780-787.

There is great interest in the role of the endothelial progenitor cells (EPCs) in both health and disease. Because of their putative role in angiogenesis and vessel repair, these cells are being investigated as a therapeutic option in a number of vascular disorders, including pulmonary arterial hypertension (PAH).[1-3] However, hypotheses have suggested that these cells may play a pathologic role in some diseases.[4,5] Toshner et al has recently investigated whether EPCs could be involved in the pathologic lesions present in the precapillary vasculature of patients with PAH.

The authors identified increased markers of EPCs (CD133 and c-Kit) as well as the homing signal pathway stromal cell-derived factor-1 and its chemokine receptor (CXCR4) within lung tissue, particularly within the plexiform lesions, of patients with idiopathic PAH, familial PAH, and PAH associated with congenital heart disease. They also identified increases in circulating angiogenic progenitor cells in the peripheral blood of patients with PAH by flow cytometry. Lastly, they reported that late outgrowth progenitor cells from patients with PAH and associated BMPRII mutations had an abnormal, "hyperproliferative" growth pattern and impaired ability to form vascular networks. Interestingly, the number of peripheral EPCs did not correlate with cardiopulmonary hemodynamics such as pulmonary artery pressure, cardiac index, or pulmonary vascular resistance.

The function of EPCs in health and disease remains an area of great scientific and clinical interest. However, there is clearly a lot yet to learn about these cells. This study raises some important questions about their role in the disease process of PAH.

References

1. Zhao YD, Courtman DW, Deng Y, Kugathasan L, Zhang Q, Stewart DJ. Rescue of monocrotaline-induced pulmonary arterial hypertension using bone marrow-derived endothelial-like progenitor cells: efficacy of combined cell and eNOS gene therapy in established disease. *Circ Res.* 2005;96:442-450.
2. Takahashi M, Nakamura T, Toba T, Kajiwara N, Kato H, Shimizu Y. Transplantation of endothelial progenitor cells into the lung to alleviate pulmonary hypertension in dogs. *Tissue Eng.* 2004;10:771-779.
3. Wang XX, Zhang FR, Shang YP, et al. Transplantation of autologous endothelial progenitor cells may be beneficial in patients with idiopathic pulmonary arterial hypertension: a pilot randomized controlled trial. *J Am Coll Cardiol.* 2007;49:1566-1571.
4. Allegra A, Coppolino G, Bolignano D, et al. Endothelial progenitor cells: pathogenetic role and therapeutic perspectives. *J Nephrol.* 2009;22:463-475.
5. Shaked Y, Voest EE. Bone marrow derived cells in tumor angiogenesis and growth: are they the good, the bad or the evil? *Biochim Biophys Acta.* 2009;1796:1-4. ■