Depression and Pulmonary Arterial Hypertension: Should We be Screening for Depressive Symptoms?

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Pulmonary arterial hypertension (PAH) is a rare and debilitating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance, leading to right ventricular failure and death.[1-4] As there is no cure, the primary goal of disease management is to alleviate symptoms and prolong survival. Although treatment of patients with PAH with agents such as prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors has been shown to improve exercise capacity,[5] many patients still experience diminished quality of life, severe limitations in mobility requiring lifestyle modifications, and a potential for social isolation. Treatment for PAH can be complex and expensive, creating a heavy financial burden on PAH patients. The physical burden imposed by PAH may result in loss of work, adding to the worry about paying for expensive therapies. Despite improvements in the treatment of PAH, patients still suffer from the uncertainty of this progressive disease. Thus, patients with PAH can accumulate a number of life stressors, which have been associated with the development of depression.[6] Furthermore, the common PAH symptom of decreased exercise capacity is strongly associated with depression in other disease states.[7-9] Due to diminished quality of life, decreased mobility, social isolation, financial burdens, unemployment, and an uncertain prognosis, patients with PAH may be more vulnerable to developing depression.

According to the World Health Organization (WHO), depression is the leading cause of disability as measured by Years Living with a Disability,[10] and organizations such as the Institute of Medicine emphasize that depression screening and treatment should be a priority for US medicine in the 21st century.[11] Clinical depression frequently causes major functional impairment that interferes with a person's ability to perform activities of daily living.[12] Major depressive disorder is estimated to have a prevalence in the general population of approximately 5%-6%.[13] A diagnosis of major depressive disorder requires the presence of 5 or more of the following symptoms most days of the week most of the time for a minimum of 2 weeks: 1) depressed or irritable mood; 2) markedly diminished interest or pleasure in all or nearly all activities; 3) significant weight loss or gain, or a decrease or increase in appetite; 4) insomnia or hypersomnia; 5) psychomotor agitation or retardation; 6) fatigue or loss of energy; 7) feelings of worthlessness or excessive or inappropriate guilt; 8) diminished ability to think or concentrate or indecisiveness; or 9) recurrent thoughts of death, suicidal ideation, or suicide attempt. One of the symptoms must include depressed or irritable mood, or loss of interest or pleasure, and the symptoms must cause either significant clinical distress or functional impairment.[14]

It seems likely that a severe, progressive, chronic illness like pulmonary hypertension would increase the prevalence of depressive symptoms. Our clinical experience, as well as the literature available to date, supports this supposition. For example, the REVEAL Registry™, a recent multicenter observational cohort study of WHO Group 1 PAH, found that 25% of patients report a history of depression.[15] This finding was based on patient self-reporting, rather than utilization of a standardized assessment instrument with good sensitivity and specificity for measuring the presence and severity of depressive symptoms. A survey from Lowe et al[16] found that at least one-third of pulmonary hypertension patients suffer from a common and potentially treatable mental disorder, with the major depressive disorders observed in 15.9%, while another study[17] estimated 26% of PAH patients had moderate to severe symptoms of depression. While the prevalence of depression in medically ill populations varies widely according to the definition of depression and the types of assessment measures used, for patients whose symptoms are explained by organic disease, the prevalence of depressive disorder in medical outpatients is 4%-12%.[18]

Patients with left-sided cardiac failure experience physical symptoms similar to those of pulmonary hypertension patients, including dyspnea on exertion, exercise limitation, fluid retention, difficulty sleeping, and fatigue. It is likely that similar symptoms increase the prevalence of depressive symptoms in patients with PAH and associated right-sided cardiac disease. The prevalence of depressive symptoms in outpatients with left-sided cardiac failure is estimated to be approximately 30%,[19] and in this population, depressive symptoms have a significant impact on functional status and quality of life.

Although there are few published data on the impact of depressive disorders on outcome in patients with PAH and right-sided cardiac disease, there has been considerable research

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demonstrating the deleterious effects of depression on morbidity and mortality in patients with left-sided cardiac failure. In left-sided congestive heart failure, although depressed and nondepressed patients demonstrate no significant difference in baseline cardiac function, depressed patients are at significantly higher risk for worsening of their heart failure symptoms, physical functioning, and quality of life, with depressive symptoms being the strongest predictor of decline in health status.[19] Similarly, after acute coronary syndrome, patients with depressive symptoms have more frequent angina (odds ratio 2.40, $P<0.001$), greater physical limitation (odds ratio 2.89, $P<0.001$), and worse quality of life (odds ratio 2.84, $P<0.001$).[20] Moreover, after acute myocardial infarction, depression is associated with increased mortality.[21] In their study of coronary disease, Ruo et al[8] found that depressive symptoms, when controlling for cardiac function, were strongly associated with overall and disease-specific health status and with health status outcomes, including symptom burden, physical limitation, quality of life, and overall health. It has also been shown in multiple studies that the presence of depression and other negative psychosocial factors are predictive of developing cardiovascular disease.[22]

Of note, clinical studies of left-sided cardiac failure have often examined depressive symptoms, rather than major depressive disorder as defined by DSM-IV criteria. In general, the prevalence of depressive symptoms can be expected to be higher than the prevalence of major depressive disorder. We should therefore not limit our attention to patients meeting the definition of major depressive disorder, but should also attempt to recognize the presence of less severe depressive symptoms, which can be addressed proactively.

Implications for Practice

Although it is likely that many PAH patients experience symptoms of depression, formal screening for and treatment of this disorder is not currently a common practice in pulmonary hypertension referral centers. In his survey of depression in pulmonary hypertension patients, Lowe et al found that only 24.1% of pulmonary hypertension patients diagnosed with mental disorders, including anxiety and depression, were receiving psychopharmacological or psychotherapeutic treatment.[16] This under-treatment of anxiety and depression is similar to that in other chronic, debilitating medical conditions.[23] But if our goal is to provide excellent patient-focused, high-quality care, the assessment of a patient's psychological status is an important component of the overall evaluation given the high likelihood of depressive symptoms in PAH patients. If health care providers are not screening for depressive disorder, an important piece in the care of PAH patients is likely missing, particularly if it is found that, as with left-sided cardiac failure, comorbid depression is associated with increased morbidity and mortality in PAH.

Patients often view their pulmonary hypertension clinical team as their primary care providers, and this can become a difficult expectation to fulfill. However, as most patients are seen in pulmonary hypertension clinics every 3 to 6 months, pulmonary hypertension health care providers are well positioned to recognize and address concurrent psychiatric illness. Often, nurses are the first to recognize clues from the patient that he or she might be suffering from depression. For example, during a clinical intake, the patient may express his or her sense of hopelessness to the nurse by saying "I just don't feel like taking my medicines anymore; I don't see the point in it." After further questioning, the patient may report the feeling that he or she can't talk to a spouse about symptoms, or express major financial concerns regarding the costs of pulmonary hypertension medications. Patients also frequently express concerns about an inability to lose weight since becoming ill. Ideally, the astute nurse picks up that there might be a problem, and passes this information on to the physician, who then further assesses the patient's psychological status using a standardized screening measure as described below. The patient is then referred to a psychiatrist or other mental health professional as needed, or if the provider is comfortable starting treatment for depression, treatment is initiated and referral for follow-up care is made.

Unfortunately, however, the realities of current medical care are such that inadequate assessment for depression and other comorbid psychiatric disorders is the rule rather than the exception. In a busy pulmonary hypertension practice, clinic time with each patient is limited, patients need to be assessed rapidly, tests need to be ordered, and very little time remains to be spent with the patient. Additionally, physicians generally are not adequately trained on the importance of mind-body interaction and impact of comorbid psychiatric disorders on morbidity, mortality, and treatment adherence.[24] Historically, most physicians were trained using models of care that emphasized biologically based etiologic disease explanations and treatments requiring diagnostic assessments based on objective measures of illness. Such an orientation has often led to decreased interest and confidence among physicians in assessing for comorbid psychiatric illness and psychosocial factors, often influencing treatment response, such as depression, anxiety, social support, and quality of life, which have frequently been perceived by many doctors to be part of a less medical, more qualitative, "softer" science. Possible evidence for the adverse consequences of such an approach is described in the heart failure literature; in spite of the plethora of studies on left-sided cardiac failure showing a relationship between depression and increased morbidity and mortality, there is very infrequent assessment for and treatment of comorbid mental disorders in cardiology clinical practices.[24,25]

Screening

Abundant evidence exists that depression-screening assessments have been successfully used in large medical practices to accurately identify depressed individuals. Increased use of such instruments should be considered in the assessment of patients with PAH. A standardized tool that has been used in a variety of clinical settings is the Patient Health Questionnaire (PHQ-8).[26] It consists of 8 brief questions, is easy to use, and takes less than 2 minutes for the patient to complete (see **Figure 1**). The patient can fill it out in the waiting or exam room, and a nurse or physician can quickly add up the score. Although various cut-offs have been proposed and found to be useful in identifying individuals with clinically significant depressive symptoms, a PHQ-8 score of ≥ 10, which has a high sensitivity for identifying major depressive disorder, alerts the provider that further investigation is needed to more comprehensively assess whether a patient is suffering from depression.[26] Even lower scores can be indicative of clinical depression because there is considerable evidence that subsyndromal depression causes as much clinical distress and functional impairment as most of the common chronic medical disorders seen in primary care practices.[27]

Patient Health Questionnaire (PHQ-8)

Name: _____ Date: _____

Over the last 2 weeks, how often have you been bothered by any of the following problems?

(use "✔" to indicate your answer)

	Not at all	More than several days	Nearly half the days	Every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself or that you are a failure or have let yourself or family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

Add Columns: _____ + _____ + _____ + _____

Total: _____

From the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MDPHQ).
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Figure 1

Treatment

Once a patient is found on screening to have symptoms suggestive of clinically significant depression, a system to ensure appropriate evaluation, treatment, and follow-up is essential. Because of the stigma often associated with a diagnosis of depression and mental disorders in general, it is important for the provider to give psycho-education to the patient, emphasizing that, like PAH, depression is a medical illness with significant morbidity and mortality, as well as a potential risk factor for worse prognosis of the primary medical illness. Patients should also be told that recovering from depression is not simply a question of "will" since it is believed, based on current research data, that biological, psychological, and social factors can lead to dysregulation of neurotransmitters and other systems in the brain.[14]

Patients suspected of having depression should undergo a formal evaluation to establish the presence of a depressive disorder and determine the appropriate type and level of treatment. An important component of any evaluation includes assessment of risk for suicide, which is a major complication of depression. In addition, depressed individuals frequently suffer from other psychiatric illnesses, such as anxiety disorders and substance depen- dence, which may be contributing to or exacerbating the depression.

Given the wide range of depression severity and complexity in diagnosing and treating it, multiple treatment options must be available to optimally treat each patient. To some extent, choice of psychotherapy and/or medications may depend on available resources and patient preferences. In addition, providers vary in their knowledge and comfort level when it comes to prescribing antidepressant medication for their patients.

For milder cases of depression requiring only medication management, the primary care physician may be able to provide treatment. In more complex, severe cases with extensive psychiatric comorbidity and concerns about suicide, referral to a psychiatrist or other mental health professional is indicated. In some practices, there are mental health professionals on-site to evaluate and treat patients. In other settings, close relationships are sometimes forged between primary care physicians and mental health professionals, which can help to effectively coordinate the treatment of the patient's primary medical illness and comorbid depression.

Currently, there are multiple FDA-approved medications for the treatment of major depressive disorder. Psychosocial treatments, such as cognitive-behavioral therapy and interpersonal therapy, have been shown to be highly efficacious in the treatment of this illness.

Promising new interventions with less of an evidence base are also proliferating and should be considered as possible interventions. For example, there has been a growing recognition that patients with severe, chronic medical illnesses may benefit from support groups in which other individuals with the same illness can be a positive support because they may have empathy for the patient's suffering that only comes from having the same illness. Others with the illness may also be able to offer guidance on how they have learned to cope with many of the challenges that PAH patients face. And in the age of the Internet, online chat rooms may also enable patients to share their experiences and decrease their sense of isolation.

Another promising, potentially beneficial new intervention for depression is exercise, which has also been shown to reduce stress and anxiety.[28] Because of the potential risk for adverse events (ie, syncope, sudden death), PAH patients have historically been counseled to avoid exercise. Yet the REVEAL Registry™ shows that some PAH patients are overweight, with an average BMI of 28.9.[15] A randomized, 15-week, closely-monitored program of daily exercise done in patients with severe pulmonary hypertension was completed by Mereles et al,[29] and showed that exercise capacity and quality of life were significantly enhanced in the exercise training group. It seems that exercise may be a logical therapy for the psychological disorders experienced by PAH patients, but studies need to be done to assess its efficacy and safety in patients with PAH and to determine the best type and intensity of exercise that will optimally alleviate symptoms of depression.

The Future

Further research on depression in PAH is needed. Many unanswered questions remain. First, the prevalence of depressive symptoms in PAH patients must be determined. The limitation of using the REVEAL Registry™, which captures depression by patient self-reporting, is that a larger group of patients who are potentially "at-risk" with moderate depressive symptoms and who may benefit from treatment may be missed. A recently completed small pilot study has been presented in abstract form describing a high prevalence of depressive symptoms in 100 patients at 2 large PAH centers,[30] using the PHQ-8 assessment tool as previously described, and replicating and expanding upon the results of earlier studies. There is now sufficient evidence of an association between depression and PAH in these pilot studies to suggest that a larger multicenter study is warranted.

Other important questions include: What are the associations between depressive symptoms and functional capacity? Are they dependent or independent of one another? Is depression a risk factor for worsening PAH, as has been shown in heart failure, or is depression a secondary event elicited by the inevitable decline in functional capacity? Would treatment of depression in PAH make a difference in survival? If, as has been found in left-sided cardiac disease, the occurrence of depressive symptoms in patients with PAH has a significant impact on functional status and quality of life, as well as risk for worsening of symptoms, early detection of depression and implementation of appropriate treatment could have a significant impact on overall outcomes in PAH patients. Is there a preferred antidepressive medication for PAH patients? Given the recent data[31,32] showing the potential association of decreased mortality and decreased development of PAH with SSRI use when treating adults, one can't help but wonder whether SSRIs are of potential benefit. Are nondrug therapies (ie, cognitive behavioral therapy, interpersonal therapy, supportive therapy, psycho-education, support groups, pulmonary rehabilitation, counseling) as effective or more so than drug therapy in PAH patients? Is a combination of medication and psychosocial treatments necessary to achieve good outcomes, as has been shown in certain subgroups of depressed individuals without medical illness?

Recognition and treatment of patients with depressive symptoms will likely improve PAH patients' quality of life, and this should propel clinicians to screen for the disorder routinely. Screening for this important comorbidity will contribute to comprehensive care for our patients, and improve overall outcome.

References

1. Simonneau G, Rubin LJ, Galiè N, et al; PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med*. 2008; 149(8):521-530.
2. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med*. 2004;351(16):1655-1665.
3. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation*. 2006;114(13):1417-1431.
4. McLaughlin V, Humbert M, Coghlan G, Nash P, Steen V. Pulmonary arterial hypertension: the most devastating vascular complication of systemic sclerosis. *Rheumatology (Oxford)*. 2009;(48 Suppl 3):iii25-iii31.
5. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest*. 2007;131(6):1917-1928.
6. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry*. 1999; 156(6):837-841.
7. Janson C, Björnsson E, Hetta J, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. *Am J Respir Crit Care Med*. 1994; 149(4 Pt 1):930-934.
8. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA*. 2003;290(2):215-221.
9. Al-shair K, Dockry R, Mallia-Milanes B, Kolsum U, Singh D, Vestbo J. Depression and its relationship with poor exercise capacity, BODE index and muscle wasting in COPD. *Respir Med*. 2009;103(10):1572-1579.
10. Depression. World Health Organization Web site. http://www.who.int/mental_health/management/depression/definition/en/. Accessed December 15, 2009.
11. Adams K, Corrigan JM, eds. *Priority Areas for National Action: Transforming Health Care Quality*. Washington, DC: The National Academies Press; 2003:1-14.
12. Seligman L. *Selecting effective treatments: a comprehensive systematic guide to treating mental disorders*. 3rd ed. San Francisco: Jossey-Bass; 2007:180-233.
13. Kessler RC, Chiu WT, Demier O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617-627.
14. Mood Disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. *Text Revision*, Washington, DC: American Psychiatric Association; 2000:345-428.
15. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary Arterial Hypertension: Baseline Characteristics From the REVEAL Registry. *Chest*. 2009 Oct 16. [Epub ahead of print]
16. Löwe B, Gräfe K, Ufer C, et al. Anxiety and depression in patients with pulmonary hypertension. *Psychosom Med*. 2004;66(6):831-836.
17. White J, Hopkins RO, Glissmeyer EW, Kitterman N, Elliott CG. Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension. *Respir Res*. 2006;7:55.

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. ■