

Stem Cells and Hypertension: Another Challenge for the Future?

MARIA E. MARKETOU, PANOS E. VARDAS

Cardiology Department, Heraklion University Hospital, Crete, Greece

Key words: **Stem cells, endothelial progenitor cells, hypertension.**

Address:
Maria E. Marketou

Cardiology Department
Heraklion University
Hospital
P.O. Box 1352
71110 Heraklion
Crete, Greece
e-mail: maryemarke@yahoo.gr

Arterial hypertension is a disease of the heart and blood vessels, which adapt their structure and function to the increased pressure loads. Hypertension starts with endothelial dysfunction and progresses gradually to hypertrophy and remodelling of both the cardiac cavities and the peripheral vessels. These changes initially balance out, but later they lead to a vicious circle of deterioration and decline in cardiovascular function. Thus, hypertension is one of the basic risk factors for coronary artery disease, heart failure, and peripheral artery disease, greatly increasing cardiovascular mortality.

In recent years, there has been much discussion about the role and the future of stem cells and progenitor cells in the pathophysiology and treatment of cardiovascular disorders. Embryonic stem cells and stem cells from adults are very promising future therapies for various diseases. Embryonic stem cells can be transformed into various cell series, either *in vitro* or when transplanted into the heart. However, their use raises many technical and ethical issues that have not yet been resolved. Most of the existing data concern adult stem and pluripotent cells in patients with acute myocardial infarction, or heart failure of ischaemic or idiopathic origin. More specifically, after an acute myocardial infarction the production of stem cells, and in particular endothelial progen-

itor cells, is increased and they are mobilised from bone marrow to assist in the better healing of the myocardium. Their presence has been found to be inversely related to the size of the infarct and directly related to left ventricular function.^{1,2}

The growing body of research in this area has produced more and more encouraging results. Clinical applications still face problems, since the role of these cells is complex and dependent on many mechanisms; however, we already have a much better understanding of the pathophysiology of cardiovascular disorders.

Endothelial dysfunction and progenitor cells

Endothelial disorders and the loss of endothelial cells are prominent phenomena in cardiovascular diseases. Especially in hypertensive patients, the changes that occur in the endothelium are large, early, and precede the permanent lesions in the vascular wall. These changes lead to an increase in peripheral resistances and reduced vascular relaxation because of endothelial cell dysfunction. Since endothelial dysfunction is one of the early events in hypertensive patients and the improvement of endothelial properties has become the target of much research, it is natural that the spotlight should have fallen on endothelial progenitor cells.

Endothelial progenitor cells participate in the process of re-endothelisation

as soon as they become established in the vascular wall.³ We know that damaged cells there are replaced by stem cells that are mobilised from bone marrow and converted into endothelial progenitor cells, while it has been suggested that disturbances of this process are associated with the process of vascular remodelling and endothelial dysfunction.⁴ It seems, however, that factors such as age, or risk factors for coronary artery disease, reduce the capacity for this kind of re-endothelialisation.^{5,6} On the other hand, mobilisation of mesenchymal stem cells leads to intimal hyperplasia of the vessels and arteriopathy.^{7,8}

Progenitor cells and hypertension

In the heart, an increase in preload leads to the mobilisation of progenitor cells from bone marrow for use in neovascularisation, which plays an important role in cardiac hypertrophy.⁹ Similarly, resident precursor cells, which are already present in the heart and are activated by the developmental programme through various molecular pathways, are also considered to play an important role in remodelling of the cardiac muscle.¹⁰ A study of hypertensive patients in our department showed that the expression of genes such as myocardin and GATA4, which are related to the presence of mesenchymal progenitor cells in peripheral blood and their differentiation into cells of the cardiac series, is increased and has an association with both the blood pressure levels and the left ventricular hypertrophy that these patients exhibit.¹¹

In the very early stages of hypertension, before the appearance of structural changes in the vascular wall, we already see a significant increase in circulating progenitor cells that is associated with reactive oxygen species and oxidative stress.¹² The purpose of this is to maintain a sufficient concentration of endothelial progenitor cells for repair of the vascular wall lesions caused by the pathological haemodynamic and biochemical factors that have been described in hypertensive patients. The endothelial cells circulate in peripheral blood – though only in small numbers – and are responsible for neovascularisation in adults.^{13,14} They can proliferate and differentiate into endothelial cells and can heal the vascular wall. Vasa et al studied patients with coronary artery disease and found that in those who also had hypertension the migratory capacity of endothelial progenitor cells was reduced, although their total number did not change significantly.⁵ Indeed, the authors showed that hypertension is the risk factor that, more than any other,

disturbs the normal migratory capacity of endothelial progenitor cells. Experiments have shown that when endothelial cells are exposed to increased mechanical pressures they “age” prematurely and are replaced by new endothelial cells that originate from differentiated stem cells.¹⁵ On the other hand, a firm correlation between the numbers of these cells and blood pressure levels has not been established, with some studies finding statistical significance and others not. One study of patients with malignant hypertension who exhibited micro- and macrovascular dysfunction reported an increased number of circulating endothelial cells and endothelial progenitor cells, even when the blood pressure was well controlled.¹⁶ However, the role of progenitor cells in hypertension has not been sufficiently elucidated, and one could argue that the reverse also applies: namely, the disturbances in the function and the number of progenitor cells occur first, and lead to a reduction in the organism’s reserves for repair of endothelial damage – wherever it may be – endothelial dysfunction and the appearance of hypertension.

Certainly, the use of stem cells as a therapeutic challenge in hypertension is still in its infancy and has mainly been confined to experimental models of cardiac hypertrophy. In mice with myocardial hypertrophy caused by angiotensin infusion it has been found that stem cell administration through the umbilical cord resulted in reversal of the hypertrophy and the conditions that led to heart failure.¹⁷

Stem cells and the renin-angiotensin-aldosterone system

Although the overall picture is still not clear, it appears that angiotensin II plays an important role in all this. We know that angiotensin II dramatically reduces the activity of the telomerase enzyme – which lengthens telomeres – in endothelial progenitor cells and accelerates their senescence via an increase in oxidative stress. However, it seems that, more generally, angiotensin causes damage to these cells’ DNA.¹⁸ The renin-angiotensin-aldosterone system is implicated in the dysfunction of these progenitor cells and inhibits their proliferation, phenomena that are countered to some degree by the presence of angiotensin receptor antagonists.¹⁹ However, experiments by the same group of investigators who demonstrated these effects suggest that angiotensin may actually increase the proliferation of endothelial progenitor cells when those cells are also incubated with vascular endothelial growth factor. Although in itself it reduces their

proliferation, it boosts their induction by vasculogenic agents via an increase in receptors such as kinase domain receptor.²⁰

Animal experiments have shown that two weeks' therapy with candesartan in hypertensive rats restored the number and the function of endothelial progenitor cells.²¹ In clinical studies, the administration of angiotensin receptor blockers, such as irbesartan or olmesartan, to patients with type 2 diabetes mellitus significantly increased the number of endothelial progenitor cells but not CD34+ haematopoietic stem cells.²² Also, the administration of angiotensin-converting enzyme inhibitors, such as ramipril, for one month in patients with coronary artery disease improved the functional properties of endothelial progenitor cells and increased their number about 2.5-fold, independently of the effect the drug had on blood pressure.²³ These findings may be related to the beneficial effects of these cells on vascular endothelial function in hypertensive patients.

In addition, via the activation of the angiotensin type 1 receptors in these cells, they are also able to differentiate into smooth muscle cells in the vascular wall, a phenomenon that is diminished by the administration of angiotensin receptor blockers, leading to a reduction in vessel hyperplasia.²⁴ Similar effects to those of angiotensin II are also seen to result from the administration of aldosterone in animals, which inhibits the function, the differentiation and the proliferation of progenitor cells, mainly via an increase in oxidative stress.²⁵ Finally, it has been reported that the B2 bradykinin receptor is expressed to a great degree in CD34+ and CD133+ as well as in early endothelial progenitor cells, while bradykinin itself is for them a powerful chemotactic agent.²⁶

In conclusion, stem and progenitor cells have great clinical significance in the pathophysiology of hypertension, as well as in its progression to heart failure and atheromatosis. It is likely that, in the future, these cells will be the target of a therapeutic approach aimed at preventing or reversing target organ lesions.

References

1. Valgimigli M, Rigolin GM, Cittanti C, et al. Use of granulocyte-colony stimulating factor during acute myocardial infarction to enhance bone marrow stem cell mobilization in humans: clinical and angiographic safety profile. *Eur Heart J*. 2005; 26: 1838-1845.
2. Valgimigli M, Rigolin GM, Fucili A, et al. CD34+ and endothelial progenitor cells in patients with various degrees of congestive heart failure. *Circulation*. 2004; 110: 1209-1212.
3. Kong D, Melo LG, Gnecci M, et al. Cytokine-induced mobilization of circulating endothelial progenitor cells enhances repair of injured arteries. *Circulation*. 2004; 110: 2039-2046.
4. Coppolino G, Bolignano D, Campo S, Loddo S, Teti D, Bucemi M. Circulating progenitor cells after cold pressor test in hypertensive and uremic patients. *Hypertens Res*. 2008; 31: 717-724.
5. Vasa M, Fichtlscherer S, Aicher A, 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. Rauscher FM, Goldschmidt-Clermont PJ, Davis BH, et al. Aging, progenitor cell exhaustion, and atherosclerosis. *Circulation*. 2003; 108: 457-463.
7. Bergmann MW. WNT signaling in adult cardiac hypertrophy and remodeling: lessons learned from cardiac development. *Circ Res*. 2010; 107: 1198-1208.
8. Caplice NM, Bunch TJ, Stalboerger PG, et al. Smooth muscle cells in human coronary atherosclerosis can originate from cells administered at marrow transplantation. *Proc Natl Acad Sci U S A*. 2003; 100: 4754-4759.
9. Müller P, Kazakov A, Semenov A, Böhm M, Laufs U. Pressure-induced cardiac overload induces upregulation of endothelial and myocardial progenitor cells. *Cardiovasc Res*. 2008; 77: 151-159.
10. Sata M, Saiura A, Kunisato A, et al. Hematopoietic stem cells differentiate into vascular cells that participate in the pathogenesis of atherosclerosis. *Nat Med*. 2002; 8: 403-409.
11. Kontaraki JE, Marketou ME, Zacharis EA, Parthenakis FI, Vardas PE. Early cardiac gene transcript levels in peripheral blood mononuclear cells in patients with untreated essential hypertension. *J Hypertens*. 2011; 29: 791-797.
12. Mandraffino G, Sardo MA, Riggio S, et al. Circulating progenitor cells are increased in newly diagnosed untreated hypertensive patients with arterial stiffening but normal carotid intima-media thickness. *Hypertens Res* 2011; May 19 [Epub ahead of print].
13. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science*. 1997; 275: 964-967.
14. Crosby JR, Kaminski WE, Schatteman G, et al. Endothelial cells of hematopoietic origin make a significant contribution to adult blood vessel formation. *Circ Res*. 2000; 87: 728-730.
15. Félétou M, Vanhoutte PM. Endothelial dysfunction: a multifaceted disorder (The Wiggers Award Lecture). *Am J Physiol Heart Circ Physiol*. 2006; 291: H985-1002.
16. Shantsila A, Dwivedi G, Shantsila E, Butt M, Beevers DG, Lip GY. Persistent macrovascular and microvascular dysfunction in patients with malignant hypertension. *Hypertension*. 2011; 57: 490-496.
17. Vanamala SK, Gopinath S, Gondi CS, Rao JS. Effect of human umbilical cord blood cells on Ang-II-induced hypertrophy in mice. *Biochem Biophys Res Commun*. 2009; 386: 386-391.
18. Herbert KE, Mistry Y, Hastings R, Poolman T, Niklason L, Williams B. Angiotensin II-mediated oxidative DNA damage accelerates cellular senescence in cultured human vascular smooth muscle cells via telomere-dependent and independent pathways. *Circ Res*. 2008; 102: 201-208.
19. Imanishi T, Hano T, Nishio I. Angiotensin II accelerates endothelial progenitor cell senescence through induction of oxidative stress. *J Hypertens*. 2005; 23: 97-104.
20. Imanishi T, Hano T, Nishio I. Angiotensin II potentiates vas-

- cular endothelial growth factor-induced proliferation and network formation of endothelial progenitor cells. *Hypertens Res.* 2004; 27: 101-108.
21. Yu Y, Fukuda N, Yao EH, et al. Effects of an ARB on endothelial progenitor cell function and cardiovascular oxidation in hypertension. *Am J Hypertens* 2008; 21: 72-77.
 22. Bahlmann FH, de Groot K, Mueller O, Hertel B, Haller H, Fliser D. Stimulation of endothelial progenitor cells: a new putative therapeutic effect of angiotensin II receptor antagonists. *Hypertension.* 2005; 45: 526-529.
 23. Min TQ, Zhu CJ, Xiang WX, Hui ZJ, Peng SY. Improvement in endothelial progenitor cells from peripheral blood by ramipril therapy in patients with stable coronary artery disease. *Cardiovasc Drugs Ther.* 2004; 18: 203-209.
 24. Yamada T, Kondo T, Numaguchi Y, et al. Angiotensin II receptor blocker inhibits neointimal hyperplasia through regulation of smooth muscle-like progenitor cells. *Arterioscler Thromb Vasc Biol.* 2007; 27: 2363-2369.
 25. Thum T, Schmitter K, Fleissner F, et al. Impairment of endothelial progenitor cell function and vascularization capacity by aldosterone in mice and humans. *Eur Heart J.* 2011; 32: 1275-1286.
 26. Kränkel N, Katare RG, Siragusa M, et al. Role of kinin B2 receptor signaling in the recruitment of circulating progenitor cells with neovascularization potential. *Circ Res.* 2008; 103: 1335-1343.