The formation of new capillaries to provide oxygen supply for ischemic tissues or tumors was believed to be exclusively mediated by the proliferation and migration of existing endothelial cells. However, increasing evidence suggests that circulating cells home to sites of ischemia and contribute to adult neovascularization. It is likely that these processes are of importance in the long-term evolution of vascular adaptation of patients with ischemic diseases and possibly of hypertensive patients. Actually, ischemia is a major component of most of end-target damages of hypertension; thus, treatments and/or nonpharmacological therapy (such as physical exercise training for example) aiming to promote neovascularization could have new and unexpected beneficial effects.

Bahlmann et al report, in this issue of Hypertension, that treatment with angiotensin II receptor antagonists increases the number of regenerative endothelial progenitor cells (EPCs) in patients with type II diabetes.1

What Are the EPCs?
In 1997, Asahara et al reported that CD34-positive mononuclear cells in the human peripheral blood incorporated into the foci of vascular injury and differentiated into vascular endothelial cells.2 Labeled human CD34-positive mononuclear cells isolated from peripheral blood and administered to nude mice with ischemic hindlimb were able to be incorporated into the ischemic muscle tissue and differentiated into endothelial cells. Further studies from the same group demonstrated that a certain population of bone marrow cells, now identified as EPCs, is recruited in the foci of neovascular formation and differentiates into vascular endothelial cells in the setting of both physiological (during the endometrium proliferative process for example) and pathological (surgically induced limb ischemia, myocardial infarction) neovascular formation.

The discovery of EPCs indicates that postnatal neovascularization does not rely exclusively on sprouting from pre-existing blood vessels. Instead, EPCs are derived from bone marrow to be incorporated into and thus contribute to neovascularization.

EPCs in Cardiovascular Diseases
Dimmeler et al3 reported that patients with coronary artery disease had fewer EPCs in peripheral blood. The value of risk factor score, evaluated from age, sex, hypertension, diabetes, smoking, and low-density lipoprotein cholesterol level, was significantly correlated with a reduction in EPCs blood levels.

In control non-diabetic animals, transplantation of bone marrow–mononuclear cells (BM-MNC) isolated from non-diabetic mice significantly raised the neovascularization process in the hindlimb ischemic model, whereas administration of diabetic BM-MNCs had little effect. In diabetic mice, injection of nondiabetic BM-MNCs was much more efficient than that of diabetic BM-MNCs. Such dysfunction was associated with the impairment of diabetic BM-MNCs in vitro capacity to differentiate into EPCs and to participate in vascular-like structure formation.4 In the same way, EPCs from patients with type II diabetes exhibit impaired proliferation, adhesion, and incorporation into neovascular structures.

Several clinical trials are now conducted to test the effect of administration of EPCs or BM-MNCs in ischemic tissues, ie, myocardial infarction or peripheral artery disease. The results are mainly positive but still remain to be confirmed by large scale randomized and blinded studies. In this respect, the concept of increasing EPCs proliferation, mobilization, and participation to neovascularization in ischemic tissues by conventional pharmacological treatment is particularly interesting.

Experimental and clinical studies suggested that statins activate the hypoxia-induced neovascularization process and thus could improve the prognosis of patients with ischemic diseases. More specifically, it has been shown that statins possess favorable effects on primary and secondary prevention of coronary artery diseases independently of cholesterol reduction. This is in line with the present results of Bahlmann et al, suggesting that the effect of angiotensin II receptor antagonists on circulating EPCs is independent from the blood pressure-lowering action in diabetic patients.

Beneficial cardiovascular effects of statin have been attributed to several mechanisms and pathways. Statins have been shown to beneficially modulate endothelium-derived nitric oxide bioavailability, thereby attenuating endothelial dysfunction and atherosclerotic disease progression.5 Likewise, statins prevent induction of reactive oxygen species in vascular smooth muscle cells and cardiac myocytes and contribute to their beneficial anti-inflammatory actions. Finally, statins administered to rats for 2 weeks increased circulating EPCs (2.4-fold) and participate in arterial wall repair after mechanical injury, providing evidence that EPC mobilization...
represents a functionally relevant consequence of statin therapy.  

**Angiotensin II, Inflammation, and EPCs**

Activation of the renin-angiotensin-aldosterone system is associated with type II diabetes. Therapeutic strategies such as renin-angiotensin-aldosterone system have interference proved to be beneficial in both type II diabetes treatment and prevention.

Angiotensin increases oxidative stress, inflammation, and alters endothelial function. Oxidative stress is involved in the pathogenesis of a wide range of cardiovascular diseases, including hypertension and type II diabetes. The principle sources of reactive oxygen species in the human vasculature is NAD(P)H oxidase, activated by a number of proatherogenic stimuli including angiotensin II. The resulting pro-inflammatory state may be promoted via activation of redox-sensitive transcription factors, such as nuclear factor κB and the leukocyte adhesion molecule vascular cell adhesion molecule-1, by angiotensin II-dependent pathways.

Additionally, AT1 receptor antagonists have been shown to be antioxidant and vasoprotective in patients with coronary artery disease, in relation with downregulation of vascular NAD(P)H oxidase expression. Treatment with either an angiotensin-converting enzyme inhibitor or an AT1 receptor antagonist resulted in lower levels of vascular O$_2^-$.

The results of the present study by Bahlmann et al document that angiotensin receptor antagonists increase the number of EPCs in patient with type II diabetes mellitus. This effect seems to be a class effect, because they have demonstrated it with standard doses of 2 long-acting AT1 blockers. In contrast, in patients treated with standard antihypertensives, the authors did not observe any effect on EPCs. A very recent publication suggests that angiotensin II accelerates EPC senescence via its AT1 receptor and through induction of oxidative stress. The exposure of cultured EPC to angiotensin II significantly accelerated the rate of senescence compared with a control and led to the impairment of proliferative activity. Angiotensin II-induced EPC senescence was significantly inhibited by pretreatment of either valsartan or superoxide dismutase. Angiotensin II significantly diminished telomerase activity, which critically influenced cellular senescence, although the effect was significantly reduced by pretreatment with either valsartan or superoxide dismutase.

It is now clear that EPCs are major actors in the occurrence of cardiovascular ischemic complications of several diseases including hypertension and type II diabetes. Beside the experimental and clinical trials using gene or cell therapies and aiming to understand and to evaluate new strategies, it is interesting to observe that conventional pharmacological treatments, such as statins, angiotensin type-I receptor blockers, and likely other classes of drugs, are able to mobilize EPCs and/or to increase their proliferation rate and/or to their lifetime. These actions might be of therapeutic relevance contributing to their beneficial cardiovascular effects. However, it is surprising to observe that the effect of angiotensin converting enzyme inhibition on EPCs number and activity has still not been studied. Furthermore, the precise link between EPCs concentration in peripheral blood and the cardiovascular risk in diabetic patients has not yet been determined.

**References**


Beneficial Effects of Circulating Progenitor Endothelial Cells Activated by Angiotensin Receptor Antagonists

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Hypertension. 2005;45:491-492; originally published online February 28, 2005;
doi: 10.1161/01.HYP.0000159196.10515.b5

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