

# The Role of Progenitor Endothelial Cell Dysfunction in Arterial Hypertension

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## Abstract

Hypertension remains leading cardiovascular (CV) risk factors in different population worldwide. The negative effect of hypertension on survival and CV complication partly associates with endothelial dysfunction. Recent studies have shown strong linear relation between endothelial dysfunction and morbidity and mortality in hypertensive patients. However, clear innate mechanisms contributing to target organ damages through abnormalities of vascular function are not completely understood. The lowered number and weak function of circulating endothelial progenitor cells (EPCs) is recognized new marker of endothelial dysfunction with high likely predictive value in patient populations with hypertension. The short communication is depicted the uncertain role of EPC dysfunction in pathogenesis of hypertension

**Keywords:** hypertension; endothelial dysfunction; biomarkers; endothelial progenitor cells; prediction

## Introduction

Hypertension remains a leading cardiovascular (CV) risk factor in developing and developed countries [1]. Hypertension influences on CV risk and mortality rate through target organ damages that affect vasculature particularly endothelium [2]. Endothelial dysfunction (ED) is established independent risk factor of CV complications [3]. Recent studies have shown that decreased number and altered function of circulating endothelial progenitor cells (EPCs) may be powerful marker of

ED with possible predictive value [4]. The short communication is depicted the uncertain role of EPC dysfunction in pathogenesis of hypertension.

### **Endothelial dysfunction in hypertension**

ED is determined an abnormal vascular tone reaction predominantly vasoconstriction due to potential vasodilator stimuli. ED plays a pivotal role in the development of pre-hypertension and hypertension [5]. The pathophysiological mechanisms of ED development affect several factors contributing to various faces of loss of normal vascular function and structure. The experimental models of essential hypertension have been confirmed that genetic / epigenetic factors interacting with traditional (smoking, dyslipidemia, insulin resistance, diabetes mellitus) and specific (hyperuricemia, vitamin D deficiency, elevated homocysteine levels, inflammation, oxidative stress, hypercoagulation) CV risk factors and surrounding environment may regulate vascular reparation through synthesize and release various spectrum vasoactive substances including nitric oxide (NO), involving cell mechanisms and attenuation of synthesis of pro-inflammatory cytokines, chemokines, and reactive oxygen species [6,7]. There is a large body of evidence regarding that the exhausted reparative ability of vasculature in resulting in several factors including pre-existing co-morbidities and traditional CV risk factors could be primary reasons for loss of endothelial cell integrity and shaping ED [5, 8]. In this context, endothelial progenitor cells (EPCs) that are mobbed from bone marrow precursors and peripheral tissue residences and involved in reparative processes through differentiation and turn-into mature endothelial cells are promising biomarkers of ED with possible predictive value [9].

### **The definition of endothelial progenitor cells**

The pioneer work provided by Asahara et al (1997) first reported about existing populations of circulating cells with impressive angiogenic capacities [10]. *In vitro* these cells expanded and committed to an endothelial lineage in colonies in culture, and *in vivo* after transplantation these cells have been incorporated into cores of active neovascularization demonstrating an ability to attenuate angiogenesis and vascular function through differentiation into mature microvascular endothelial cells [11]. EPCs may origin from bone marrow stem cells and human umbilical cord blood and that they may mobilize and migrate from bone marrow, differentiate into mature endothelial cells and probably smooth muscle cells of vessels, as well as synthase and realize a wide range of active molecules and growth factors (vascular endothelial growth factor, granulocyte-macrophage colony-stimulating factor) that modulate vasculogenesis and improve vascular integrity [12]. EPCs express cell markers of endothelial cells and their precursors, such as CD31, CD 144, KDR (CD309, vascular endothelial growth factor receptor-2), and CD133, but in absence of CD45. Therefore, after differentiation EPCs lose CD133 antigen and begin to be positively on CD31, vascular endothelial cadherin, endothelial NO synthase and von Willebrand factor. In fact, that specific property may allow a more precise

definition of EPCs, because majority of antigens that used as molecular markers were commonly shared with the various cells from hematopoietic lineage [11]. Depending on ability to appear in fibronectin coated dish all EPCs were divided into early outgrowth or late outgrowth endothelial cells [12]. However, there is not consensual decision regarding strong recommendation toward determining of EPCs.

### **The role of EPC dysfunction in hypertension**

EPC dysfunction is determined as weak function and / or decreased circulating number of endothelial precursors [13]. Indeed, decreased number of circulating EPCs was found a strong predictor of CV death and outcomes [14]. EPCs that circulate in the peripheral blood in patients at higher CV risk and in individuals with pre-hypertension / hypertension presented lowered survival ability and partially inconvenience to be differentiated to mature endothelial cells under influence of essential innate stimuli including transforming growth factor-beta, tumor necrosis factor-alpha and other inflammatory cytokines [15]. It has reported that EPC colony number was significantly and inversely correlated with systolic and diastolic BP in subjects with hypertension. Decreased EPC levels may contribute to the pathophysiology of microalbuminuria or macroalbuminuria in hypertensive patients with nephropathy. In patients with essential hypertension with ECG evidence of left ventricular hypertrophy (LVH) the circulating level of EPCs were lowered to those who did not have LHV [16]. In hypertensive individuals with end-stage renal disease, EPC number and function were sufficiently reduced and inversely associated with CV risk [17]. Moreover, the levels of EPCs in the peripheral blood of women with pregnancy-induced hypertension were significantly lower compared with those of control pregnant women with normal BP level [18]. Finally, lowered EPC number and altered EPC function related strongly not only with brachial BP levels, but increased central aortic systolic pressure, aortic augmentation index, and pulse wave velocity as a marker of arterial stiffness, altered brachial artery flow-mediated dilatation as a marker of endothelial dysfunction and left ventricular twisting [19].

However, the predictive role of EPC dysfunction in hypertensive individuals remains to be controversial. Although there is relation between both lowered level of circulating EPCs and reduced EPC function *in vitro* and an increased CH risk, there is not quite enough evidence regarding independent prognostication of EPC dysfunction in hypertensive population [20]. In contrast, in patients with established CAD, myocardial infarction, heart failure, cardiomyopathies, the EPC dysfunction was determined as predictor of fatal clinical outcomes [21].

In conclusion, EPC dysfunction associates with CV risk and frequently associates with a number of CV risk factors including hypertension. Whether EPC dysfunction appears in pre- hypertension is not fully clear. In this context, the independent predictive value of EPC dysfunction in hypertensive patients required to be investigated in large clinical controlled trials.

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