Are Endothelial Progenitor Cells a Prognostic Factor in Patients with Heart Failure?

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Abstract
For the last two decades, endothelial progenitor cells (EPCs) have been proposed as a novel prognostic marker and potential therapeutic target in patients with cardiovascular diseases. EPCs are involved in the process of adult vasculogenesis and repair of dysfunctional endothelium. Endothelial dysfunction has been documented in the peripheral and coronary arteries of chronic heart failure (HF) patients and has proved to be an independent predictor of morbidity and mortality in HF patients. This has led researchers to analyze the association of EPCs and disease severity in HF patients. In this paper, we review studies analyzing the prognostic role of EPCs in patients with HF. Through a systematic search, we identified fourteen relevant studies. Only one study analyzed mortality as an outcome; the others evaluated the association between EPC levels and patients’ characteristics. Overall, results were inconsistent and suggested that levels of EPCs may vary according to
Introduction
In the 1990s, it was commonly accepted that postnatal angiogenesis occurred exclusively through the local outgrowth of pre-existing vessels by means of expansion of mature endothelial cells in response to angiogenic growth factors[1]. However, an enriched population of CD34+ cells, isolated from human peripheral blood, were subsequently shown to differentiate into endothelial cells in vitro and, in mice, were incorporated into areas of angiogenesis after ischemia[2].

In the double Id1/Id3 knock-out mice, bone marrow transplant reversed the failure to grow solid tumors due to poor vascular growth, thus demonstrating the involvement of bone marrow (BM)-derived cells in angiogenesis[3]. These findings provided the first direct evidence for the role of BM-derived cells in adult neovascularization and led to the possibility of novel therapeutic targets, BM-derived cells, for tissue repair after ischemic injury.

With the discovery of circulating BM-derived cells that contribute to the formation of new vessels, a radical change in the understanding of angiogenesis occurred. This new concept has led researchers to explore the role of this group of cells, known as “endothelial progenitor cells” (EPCs), in a variety of diseases in which endothelial function and angiogenesis constitute key aspects of pathogenesis. Endothelial dysfunction is implicated in the pathogenesis of heart failure and accumulating data have demonstrated the prognostic value associated with this abnormality. This paper summarizes current evidence from clinical studies analyzing the association and potential therapeutic role of EPCs in patients with heart failure. We will not discuss the appropriateness of the nomenclature and identification of EPCs. We will use the most common definition of EPCs.

Identification of endothelial progenitor cells
The term “endothelial progenitor cells” has commonly been used as a label for circulating blood cells identified by the expression of certain surface antigens as well as cultured mononuclear cells. Depending on the length of the time of culture, these cells can lead to at least two different cell populations: early-outgrowth EPCs and late-outgrowth EPCs.

Circulating endothelial progenitor cells
Circulating EPCs are commonly characterized by the co-expression of the surface markers CD34, CD133 and VEGFR2 (vascular endothelial growth factor receptor 2). Although these markers are not unique to EPCs, it is generally accepted that their combination represents circulating EPCs [4]. Expression of CD34 was the first used to identify EPCs [2]. An important function of CD34 is cell-to-cell adhesion by binding of L-selectin. The expression of CD34 is variable and decreases as EPCs differentiate. The CD34 marker is not highly specific for EPCs as it is shared by other cells such as hematopoietic cells and mature endothelial cells [5,6]. CD133 is a five-transmembrane protein found on 20-60% of CD34+ cells. One of the identified functions of CD133 is as an organizer of membrane topology by regulating the lipid composition [7]. This marker is not expressed in mature endothelial cells. It can be also found on epithelial cells, hematopoietic and neuronal stem cells [8]. The VEGFR2, also known as KDR (kinase insert domain-containing receptor) in humans or Flk1 in rodents, is one of the three VEGFR family members. VEGFR2 is present in cells involved in vasculogenesis that can differentiate to mature endothelial cells. This receptor binds VEGF, which participates in many functions of endothelial cells, including maturation and migration [9].

The cell surface phenotype CD34+CD133+VEGFR2+ is widely used to identify presumed circulating EPC in healthy and diseased subjects. However, the small quantity of circulating EPCs makes quantification difficult. These cells represent only 0.0001-0.01% of the peripheral blood mononuclear cells [4]. For this reason, many research studies report only CD34+VEGFR2+, CD34+CD133+ or just CD34+ cells as a measure of circulating EPCs. This heterogeneity in identifying and defining EPCs makes it difficult to compare results across studies.

The origin and function of EPCs are diverse and not completely understood. Lin et al [10] explored the origin of these cells by studying 4 patients who underwent a sex-mismatched bone marrow transplant (making possible the differentiation of circulating cells with donor or recipient genotype). They found that more than 95% of circulating EPCs had a recipient genotype while the expanded culture of late-outgrowth EPCs mostly displayed a donor genotype. Based on these results, they concluded that most of the circulating EPCs are vessel derived and a small proportion are BM-derived cells with high proliferative capacity.

Several groups have examined the functional capacities of EPCs. CD34+CD133+VEGFR2+ cells do not have the capacity to form vessels in vitro nor in vivo [11]; however, they do facilitate the process of angiogenesis probably through paracrine mechanisms [12]. This evidence supports the heterogeneous composition of this group of cells and creates controversy whether or not these cells should still be labelled as EPCs since they do not form vessels directly [13].

Early-growth endothelial progenitor cells
EPCs have been cultured from cord blood, bone marrow and peripheral blood. Most researchers use density centrifugation (i.e. Ficoll centrifugation) to isolate peripheral blood mononuclear cells and then plate these cells. This assay identifies two different types of cells, early-outgrowth EPCs and late-outgrowth EPCs. Early-outgrowth EPCs are spindle-shaped cells obtained after 4-7 days of culture. Phenotypically, these cells have many characteristics of mature endothelial cells including but not limited to uptake of acetylated LDL and expression of CD34, VEGFR2, CD144, von Willebrand factor and CD31. However, these cells have limited proliferative capacity, do not form vessels directly, show phagocytic abilities and also express some hematopoietic markers such as CD45 and CD14. These features suggest that these cells represent a hematopoietic progenitor cell phenotype rather than a “true” endothelial progenitor cell phenotype [14].

Hill et al [15] modified the assay by adding a step of re-plateing the non-adherent cells after 24-48 hours of culture in order to eliminate platelets and mature endothelial cells. Studies suggest that the cells obtained from both assays have similar characteristics [14,16].

Factors such as disease severity, underlying cause of cardiomyopathy and medical therapy.
**Late-growth endothelial progenitor cells**

Late-outgrowth EPCs appear after 14 to 21 days of culture. They show cobblestone morphology, have a strong proliferative capacity, are capable of forming vascular networks and express endothelial-like markers including VEGFR2, CD34, CD146 and VE-cadherin and do not express hematopoietic cell surface markers [16]. This phenotype suggests that late-outgrowth EPCs may constitute “true” EPCs. Interestingly, a study evaluating the potential of vasculogenesis using early- versus late-outgrowth EPCs in a mouse limb ischemic injury model demonstrated that the injection of late-outgrowth EPCs had significantly higher vessel forming capacity than early outgrowth EPCs. Moreover, this capacity was further increased when the two types of cells were implanted together [17]. This finding reinforces the potential paracrine function of early outgrowth cells in the process of vasculogenesis.

**¿May EPCs play a pathogenic role in the development of heart failure?**

The main role of EPCs is to promote vasculogenesis, repair endothelial loss and dysfunctional endothelium. EPCs increase after several stimuli including surgery [18,19], myocardial infarction [20-23] and burn injury [24]; migrate to areas of ischemic injury and participate in the process of vasculogenesis [4,25-27]. Furthermore, EPCs are also associated with endothelial function. Hill et al [15] demonstrated, in individuals with no clinical coronary artery disease (CAD), higher numbers of early outgrowth EPCs were associated with lower Framingham risk scores and better endothelial function measured by brachial reactivity. Endothelial dysfunction is widely accepted as an early manifestation of atherosclerosis. Cheng et al [28] reported an independent association between low levels of early outgrowth EPCs and the presence of coronary and abdominal calcification in 889 healthy volunteers of the Framingham cohort.

Pathophysiologically, heart failure (HF) is characterized by reduced cardiac output and concomitant neuroendocrine activation. Endothelial dysfunction, defined as impaired vessel dilation to physiological stimuli, has been documented in the peripheral and coronary arteries of chronic HF patients [29-32], irrespective of the presence of CAD, and has been proposed as the cause of impaired vasodilatation in the coronary, pulmonary and peripheral vascular circulation [33]. Endothelial dysfunction is also an independent predictor of morbidity and mortality in HF patients [34,35]. It may be a critical part of the pathogenesis of HF resulting from increased oxidative stress, secondary to activation of the adrenergic/renin–angiotensin systems and to production of inflammatory cytokines [36]. Several therapies evaluated in non-randomized and randomized control trials, such as ACE inhibitors, β-blockers, statins, spironolactone, nitrates, and exercise, improve endothelial function in patients with HF. Developing a better understanding of the role of EPCs in HF, the mechanisms by which EPCs are capable of forming new vessels and repairing dysfunctional endothelium is critical in providing new insight into the complex pathophysiology of HF and potentially identifying new prognostic markers and therapeutic targets.

**Studies evaluating the role of EPCs in patients with heart failure**

Through a systematic search in Medline and references of selected studies, 14 studies that measured EPCs in patients with heart failure, utilizing any of the described assays, were identified. Twelve studies measured EPCs as circulating EPCs, using different combinations of the previously mentioned markers, and five studies measured early-outgrowth EPCs. There were no studies evaluating late-outgrowth EPCs in HF patients. One study analyzed mortality as an outcome. The remaining studies examined the relationship between levels of EPCs and patients’ characteristics including but not limited to NYHA class, type of underlying cardiomyopathy and medical therapy. To optimize clarity, presentation and discussion of studies will be according to the assay used to measure EPC levels (circulating EPCs or early outgrowth EPCs). Table 1 summarizes the main characteristics related to population, study design, criteria used to define circulating EPC and results of studies evaluating circulating and cultured EPCs in heart failure patients.
Studies measuring circulating EPCs

Valgimigli et al [37] were the first to publish an evaluation of the role of circulating EPC in HF patients. This cross-sectional study included 91 stable HF patients with impaired left ventricular ejection fraction (LVEF) and 46 sex- and age-matched healthy controls. They defined EPC according to the expression of CD34 and co-expression of CD34, CD133 and VEGFR2 antigens. They observed that NYHA class I or II patients had higher levels of circulating EPCs than healthy controls, while NYHA class III or IV patients had lower levels of EPCs. These results supported the a priori hypothesis suggesting a “protective” role of EPC in the development of cardiovascular disease. The authors hypothesized that the presence of bone marrow exhaustion may be the underlying mechanism explaining lower levels of circulating EPCs in patient with NYHA class III and IV symptoms. Their finding that EPCs were inversely correlated with tumor necrosis factor-α (TNF-α) levels, a potent bone marrow inhibiting factor, supported this hypothesis [38]. These results were corroborated by Fritzenwanger et al [39] who conducted a similar study of 101 stable HF patients and 46 unmatched healthy controls.

Nonaka-Sarukama et al [40] analyzed circulating EPCs (CD34+ cells) in 22 acutely decompensated HF patients. In this study, NYHA class I and II patients had higher EPCs levels than controls and NYHA class III and IV patients had lower levels than controls. In the hospitalized NYHA class III-IV patients, EPC levels increased in response to HF treatment achieving values similar to controls.

Based on the results of these studies, the authors alleged that circulating EPCs were associated with disease severity in HF patients and that lower EPC levels may be associated with a poorer prognosis. Results of an open-labelled randomized control trial conducted by Jie et al provided further support for the proposed causal mechanism of an exhausted BM [41]. They randomized 45 NYHA class II to IV HF patients with reduced LVEF (EF<50%) and cardiac renal syndrome (estimated creatinine clearance between 20 and 70 ml/min and mild anemia) to receive Erythropoietin (15U/kg/week) for 1 year (n=30) or continue with standard medical therapy (n=15). Although Erythropoietin has been reported to increase EPC levels [42,43], the authors found that EPCs (CD34+ and CD34+VEGFR2+) measured at 18 days and 1 year did not differ between treatment arms: in both groups, circulating EPCs showed a tendency to decrease over the year of follow up. This decrease was slightly but non-statistically significantly greater in the group of patients not receiving Erythropoietin. In addition, they found that baseline EP levels were lower than a group of healthy control individuals whom the authors studied. These observations support the hypothesis of an exhausted or suppressed BM accounting for the poor effect of Erythropoietin on EPC levels in advanced HF patients.

Based on this evidence, it was generally assumed that low levels of EPCs represent an adverse prognostic factor in heart failure. However, some studies have suggested that the nature of this association depends on the underlying cause of cardiomyopathy. Theiss et al [44] found that circulating EPCs were lower in patients with ischemic cardiomyopathy than idiopathic dilated cardiomyopathy in symptomatic HF patients with reduced LVEF but still higher than healthy controls. They did not find a correlation between NYHA class and EPC levels. In the same study, these investigators analyzed in situ concentration of homing factors including stromal cell derived factor-1 (SDF-1), hypoxia-inducible factor-1 (HIF-1) and vascular cell adhesion molecule (VCAM), in explanted hearts of transplant patients and observed that these factors were significantly upregulated (mRNA levels) in ischemic hearts but not in the myocardium from patients with dilated cardiomyopathy. This suggested an alternative hypothesis that circulating EPCs may be lower due to higher myocardial uptake and not just low generation or mobilization of EPCs in patients with ischemic cardiomyopathy. Other studies assessing only patients with CAD have reported that circulating EPCs are higher in a group of patients with reduced LVEF of whom 55% of the patients were NYHA class III-IV [45,46]. This may contradict the hypothesis that circulating EPCs are a negative prognostic factor, at least in HF patients with CAD. Prospective studies evaluating outcomes may shed light on this ambiguity.

Table 1. Studies on heart failure patients measuring endothelial progenitor cells (EPCs)

* EPCs cultured according to the Hill protocol (replating non-adherent cells at 24-48 hours)

HF, heart failure; NYHA, New York Heart Association; BNP, b-type natriuretic peptide; VO2, oxygen consumption; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; CMP, cardiomyopathy; RCT, randomized controlled trial.
Other small studies have also contradicted previous results. Carvalho et al [47] measured CD34+ cells in 23 stable HF patients and did not find an association between EPCs and NYHA class. This may be related to the small sample size and low statistical power. Geft et al [48] analyzed CD34+ cells in 58 stable HF patients and failed to find an association between EPC and disease severity. They reported that patients with advanced NYHA class had a higher percentage of CD34+ apoptotic cells. These results suggest that increased oxidative stress present in patients with HF may induce cell damage without affecting EPC levels expressing a potential role of cell quality or functional capacity as a prognostic factor associated with disease severity. In this way, decreased EPC function may represent a factor associated with poorer prognosis. The origin of these apoptotic cells still remains unknown. They may be produced within the bone marrow which has been exposed to oxidative stress or constitute cells released by the dysfunctional endothelium.

Other studies have analyzed the impact of medical therapies on circulating EPC levels in HF patients. Tousoulis et al [49] performed a randomized control trial in symptomatic HF patients with LVEF <40% who were randomized to Rosuvastatin 10 mg/day, Allopurinol 300mg/day or placebo. They reported that circulating EPCs (CD34+VEGFR2+ and CD34+VEGFR2+CD133+ cells) were increased at 1-month in the Rosuvastatin arm but not in the Allopurinol or placebo group in comparison to baseline values. They found that the increase in EPC levels was not associated with changes in the levels of inflammatory (fibrinogen, interleukin 6 and high-sensitivity C-reactive protein) and oxidative (myeloperoxidase and total lipid peroxides) markers.

Sarto et al [50] demonstrated that circulating EPCs (CD34+VEGFR2+CD31+) were increased after an 8-week anaerobic training schedule in 22 HF patients with LVEF <40%. They also described that the effect of exercise on EPC levels was not sustained since EPCs returned to baseline 8 weeks after discontinuation of the exercise activity. Craenenbroeck et al [51] found conflicting results: circulating EPCs measured as CD34+ or CD34+VEGFR2+ cells in 38 stable HF patients with LVEF <40% did not change after 6-months of anaerobic exercise training. These studies suggest that many factors may have an impact on circulating EPC levels. Discrepant results from small studies using unadjusted analysis make the interpretation of their results difficult.

In conclusion, some of the largest studies suggest that lower levels of circulating EPCs may act as a marker of disease severity. However, some studies suggest that this effect may be etiology specific and differ in patients with ischemic cardiomyopathy, gender factors such as exercise activity and statins modify EPC levels. These results support the need for larger studies using adjusted analysis to better characterize the role of circulating EPCs in HF patients. There are no studies evaluating the association between circulating EPCs and HF outcomes, such as death, cardiac transplantation or HF hospital admission. This gap in knowledge and the associated contradictory evidence make it difficult to make clear inferences.

**Studies measuring early-outgrowth EPCs**

Few studies have evaluated the role of early-outgrowth EPCs. Table 1 cites the main characteristics of these studies. Valgimigli et al [37] demonstrated that lower levels of early-outgrowth EPCs were associated with decreased functional capacity measured by NYHA.

Class in a group of stable HF patients with reduced LVEF. Similarly, an Israeli study by Shmilovich et al [52] reported a positive correlation between early-outgrowth EPCs and BNP levels in symptomatic HF outpatients. In this study, the authors also evaluated the effect of BNP on other functions of early-outgrowth EPCs from healthy individuals. They observed that cells from healthy individuals treated with BNP had increased cell adhesion and migration, in vitro tubular formation and in vivo vascularisation in a mouse hindlimb ischemia model. These results suggested proangiogenic qualities of BNP and led to a hypothesis that in patients with advanced HF and higher levels of BNP, the peripheral uptake of EPCs in areas of endothelial dysfunction and high vascular regeneration may explain the low EPC levels, similarly to Theiss et al’s hypothesis [44] to explain low EPC levels in patients with ischemic CMP. However, there is very limited evidence to support this hypothesis.

In contrast to these results, the same Israeli research group [53] had previously conducted a cohort study in 107 stable symptomatic HF patients with systolic (n=79) and diastolic dysfunction (n=28) and found no association between type of LV dysfunction (systolic vs. diastolic), underlying etiology of cardiomyopathy and levels of BNP. The authors reported that higher levels of early-outgrowth EPCs were significantly associated with all-cause mortality and impaired NYHA class. However, the number of predictors (13) in their multivariable model on mortality was high compared to the small number of outcomes reported (21 deaths). This model overfitting may lead to find untrustworthy associations just by chance.

Similarly to some observations in circulating EPCs, levels of early-outgrowth EPCs may be modified by medical therapy. Sarto et al [50] reported that cultured EPCs were increased after 8-weeks of anaerobic exercise and gradually decreased 8 weeks after cessation of exercise. Jie et al [41] reported that administration of Erythropoietin tested in a randomized control trial was not associated with changes of early-outgrowth EPC levels during 1 year follow-up.

**Role of EPCs in other cardiovascular diseases**

There is no doubt that circulating blood cells participate in vasculogenesis and vascular repair. However, there are still some areas of uncertainty. Inconsistent results are not restricted to HF patients; conflicting data also exist for example in patients with CAD. Chen at al [28] conducted one of the largest studies measuring circulating EPCs. This population based study of 889 subjects clinically free from CAD found no association between EPCs (CD34+ and CD34+VEGFR2+) and coronary and abdominal aorta calcification. However, low levels of circulating EPCs (CD34+VEGFR2+) were shown to be related to high cardiovascular risk in a cohort of 519 patients with different degrees of CAD [54]. Hristov et al [55] in a study of 144 stable CAD patients reported that initiation of statins decreased circulating EPC whereas a previous small study by Vasa et al [56] on a similar population reported a stimulating effect by statins on circulating EPCs. Similar inconsistencies occur in studies analyzing cultured EPCs. Xiao et al [58] reported that early-outgrowth EPCs were increased in patients with several cardiovascular risk factors; however other studies have reported an inverse association between early-outgrowth EPCs and arterial calcification [28] or cardiovascular events [54].
In the search for better biologic markers that can further refine our ability to prognosticate morbidity and mortality in HF patients, EPCs represent a potential new target. However, the not yet fully understood role of EPCs and the ongoing inconsistent results create uncertainty about the potential use of EPCs as a prognostic factor. There is a need for additional evidence to establish or refute the role of EPCs as a prognostic marker and therapeutic target in patients with HF.

Conclusions
EPCs represent an innovative marker with potential prognostic and therapeutic value. Even though there has been a substantial increase in the body of evidence in the last few years, further basic research studies are required to clarify the origin, function of EPCs and molecular pathways, to refine the EPC identification and characterization and to understand the process of adult vasculogenesis. In addition, higher quality clinical studies using larger sample size to allow adjusted analysis, focusing on clinically important outcomes will help to clarify the potential future use of these cells. Although initial studies have shown benefit in the treatment of myocardial infarction with EPC injection, the role of EPCs in patients with HF is unclear. Carefully designed studies analyzing their therapeutic qualities might be premature at this stage but certainly remain a possible future target based on the acquisition of a more nuanced understanding of the role of EPCs.

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**Curriculum of Dr. Ana Carolina Alba**

- She is a cardiologist from Argentina, working as a fellow in the Heart Failure/Transplant Program at the Toronto General Hospital in Canada and pursuing a doctoral degree in Clinical Epidemiology and Biostatistics in the Heath Research Methodology Program at McMaster University.
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*Note: The content seems to be a mix of medical research papers and personal curriculum information. It is presented in a way that is not clearly structured or categorized, which might make it difficult for a pure text model to accurately parse and understand.*
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- He is interested in several areas of biostatistical methodology, including: design and analysis of research studies; risk assessment and communication; evaluation of diagnostic and screening data; and regional and temporal variation in health.
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- He has acted as an Editor of the American Journal of Epidemiology, and as a Section Editor for the Wiley Encyclopedia of Biostatistics.
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- Research interest: End of life, incorporating a transplanted heart.
Publication: October 2011

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