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REVIEW

The Beneficial Effects of Cardiac Rehabilitation on the Function and Levels of Endothelial Progenitor Cells

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Cardiac rehabilitation (CR) is a comprehensive program, which mainly focusses on exercise training, disease evaluation, cardiovascular risk factors control, medication therapy, psychosocial intervention, and patient education. Although the beneficial properties of CR have been widely evidenced, its mechanism is still not completely clarified. To date, endothelial progenitor cells (EPCs) have been explored by emerging studies, and evidence has suggested that CR, especially exercise training, significantly increases the function and levels of EPCs, which is likely to elucidate the profiting mechanism of CR. Thus, this review summarises the potential relationship between CR and EPCs with an aim of providing novel directions for future CR research.

Keywords Cardiac rehabilitation • Cardiovascular disease • Exercise • Neovascularisation • Endothelial progenitor cells

Introduction

Q2 Cardiac rehabilitation (CR) is of critical importance in the secondary prevention of cardiovascular disease. It has been reported that CR was negatively related to reinfarction, cardiac morbidity and all-cause mortality [1]. Thus, CR has been listed as one of several therapeutic approaches to treat cardiovascular disease and is widely recommended in many guidelines, such as the European Society of Cardiology (ESC) Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, and the European Guidelines on cardiovascular disease prevention in clinical practice [2,3].

Cardiac rehabilitation is a program designed to reduce the morbidity and mortality of cardiovascular disorders, increase patient's exercise tolerance and psychological well-being, and improve their quality of life [4–6]. Although well-documented evidences have demonstrated the benefits of CR, its mechanism is still not elucidated.

Most cardiovascular diseases are related to endothelial injury. Endothelial progenitor cells (EPCs), a cluster of primitive cells with multiple differentiation potential, are of great importance in repairing endothelial lesions via their neovascularisation and re-endothelialisation abilities; and thereby EPCs may underlie the profiting mechanism of CR. Thus, we systematically searched PubMed as well as relevant bibliographies to identify all English-language articles examining the effects of CR on EPCs. Then we selected representative articles in every part of CR functioning on EPC levels to gain insight into the underlying beneficial mechanism of CR.

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The Predictive Role of Endothelial Progenitor Cells in Cardiovascular Disease

Endothelial progenitor cells were first isolated by Asahara et al. [7] via staining for CD34, CD133, and kinase insert domain receptor (KDR). Under physiological circumstances, EPCs mainly reside in the bone marrow, with some found in the peripheral blood. In response to a chemical or mechanical injury of the endothelium (namely tissue ischaemia and hypo-oxygen), EPCs can significantly mobilise from bone marrow into peripheral blood, then migrate to sites of injured endothelium and differentiate into mature endothelial cells [8,9]. Thereby, EPCs contribute to the intact endothelium via their capacities to proliferate, migrate and differentiate, and by serving as paracrine factories for pro-angiogenic cytokines structurally and functionally. Dysfunction of endothelial cells is associated with the pathophysiology of many cardiovascular disorders. Thus, the level of EPCs was previously seen as a predictive factor for many cardiovascular diseases [10].

Previous studies reported that hypertension was closely correlated with decreased level of EPCs. Giannotti et al. [11] isolated and assayed the function of EPCs from hypertensive patients, pre-hypertensive patients and healthy subjects, and demonstrated that the repair capacity of EPCs of hypertensive patients was substantially impaired when compared with healthy subjects. Refractory hypertension patients were identified at an even lower EPC level. Oliveras et al. [12] demonstrated that refractory hypertension patients and control subjects had EPC numbers of 33.8 and 69.1 per 10^5 peripheral mononuclear cells respectively ($p = 0.014$). After being cultured, the number of EPCs per field was reduced by 76.7% ($p < 0.001$) in refractory hypertension, which suggested a more severely impaired EPC function in refractory hypertension.

A study reported that EPC numbers in acute coronary syndrome patients were more than 2.6 times when compared with stable coronary artery disease subjects (15.6 ± 2.7 vs. $6.0 \pm 0.8/10^5$ events, $p < 0.01$), but EPCs isolated from acute coronary syndrome patients had severely impaired functions [13]. However, other studies identified patients with coronary artery disease possessing lower EPC levels. Vemparala et al. [14] measured EPC senescence levels in patients with or without angiographically documented coronary artery disease by assaying telomere length and telomerase activity. They provided evidence that the telomere length was markedly lower (3.83 vs. 5.10 kb/genome, $p = 0.009$) in premature coronary artery disease patients (age ≤ 50 years) compared with control subjects, which suggested lower EPC levels in patients with coronary artery disease. This conflicting result of EPC levels in coronary artery disease was speculated due to individual disparity, especially patients with coronary artery disease in different clinical course.

Endothelial progenitor cells levels were also expected to predict outcomes in patients with chronic heart failure. Berezin et al. [15] assessed EPC levels of various subpopulations (including CD45+CD34+, CD45-CD34+, CD14+CD309+, and CD14+CD309+Tie2+) in ischaemic chronic heart failure patients, and reported that EPC counts were negatively associated with the severity of left ventricular dysfunction. Another cross-sectional study including 121 ambulatory heart failure patients with reduced left ventricular ejection fraction had similarly concluded that circulating CD34+VEGFR2+ cells were inversely correlated with functional capacity [16]. For other cardiovascular diseases (including cardiopulmonary surgery, pulmonary arterial hypertension and peripheral artery disease), EPC levels were also reported as having important predictive values and could be used as biomarkers to some extent [17–19].

Exercise With Endothelial Progenitor Cells

Exercise plays a core role in CR program. The benefits of exercise for cardiovascular protection have been widely evidenced, and include increasing exercise capacity, controlling risk factors of cardiovascular disease, reducing inflammation, improving quality of life, and reducing morbidity and mortality [20,21]. Regular exercise at moderate intensity was reported to reduce all cardiovascular events [22]. Exercise was also identified to increase EPC levels, and data had shown that exercise increased EPCs up to four times in circulation [23].

Accumulating evidence suggested exercise improved EPC levels in cardiovascular diseases. Steiner et al. [24] investigated the effect of exercise training on patients with coronary artery disease and cardiovascular risk factors by measuring the change in their circulating EPC levels. After a 12-week supervised running training regimen, they observed that EPCs had a 2.9 ± 0.4-fold increase ($p < 0.0001$). Luk et al. [25] further assessed the impact of habitual physical activity level on coronary artery disease in patients, and concluded that physical activity level had a positive correlation with increased CD133/KDR+ EPCs. The patients with the highest physical activity levels were associated with a relative increase of 44% in EPCs compared to those in the lowest level of physical activity. A previous study also reported that patients with acute coronary syndrome participating in a CR program for four weeks had a significant improvement of inflammation markers, which was paralleled to the increase in EPC numbers [26]. Additionally, Brehm et al. [27] discussed the effects of exercise on the function and numbers of circulating progenitor cells in patients with myocardial infarction. They identified that after three weeks of exercise training, the exercise group had a significant improvement in CD45+/CD34+ circulating progenitor cells from 257 ± 102 to 302 ± 128 cells per 1 million mononuclear cells ($p = 0.022$) and the CD45+/CD133+ cells from 64 ± 26 to 88 ± 46 cells per 1 million mononuclear cells ($p = 0.023$).

For microvascular angina patients, exercise was also reported to increase EPC levels; Scalone et al. [28] tested

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