International Journal of Cardiology 166 (2013) 310–314

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

# Mending injured endothelium in chronic heart failure: A new target for exercise training

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ARTICLE INFO

*Article history:*
Received 10 September 2011
Received in revised form 13 April 2012
Accepted 16 April 2012
Available online 10 May 2012

*Keywords:*
Exercise
Training
Chronic heart failure
Endothelial dysfunction

ABSTRACT

The recognition that poor cardiac performance is not the sole determinant of exercise intolerance in CHF patients has altered the target of exercise training. Endothelial dysfunction impairs exercise-induced vasodilation, thereby limiting oxygen supply to working muscles and increasing ventricular afterload. Since the 1990s, it has become clear that partial correction of this maladaptive reaction is a premise for the success of exercise training.

Growing evidence indicates that increased NO bioavailability and reduction in oxidative stress result from regular physical activity. However, the basic concept of endothelial dysfunction has shifted from a pure "damage model" to a more dynamic process in which endothelial repair fails to keep pace with local injury. Indeed, recent evidence indicates that endothelial progenitor cells (EPC) and circulating angiogenic cells (CAC) contribute substantially to preservation of a structurally and functionally intact endothelium. In chronic heart failure, however, these endogenous repair mechanisms appear to be disrupted.

In this review, we aim to give an overview on what is currently known about the influence of physical exercise on recruitment of EPC and activation of CAC in this particular patient group.



## 1. Introduction

Fifteen million Europeans suffer from symptomatic heart failure [1]. Their main concern, besides shortened life expectancy, is poor quality of life. To a large extent, the latter is determined by exercise intolerance, which is clinically manifested by shortness of breath and fatigue [2]. Although initially a pure cardiological problem, chronic heart failure (CHF) becomes a multi-system disorder as the disease progresses [3]. Serving as an early compensatory mechanism to ensure homeostasis, chronic overactivity of the renin–angiotensin–aldosterone pathway and the sympathetic nervous system induces a vicious circle [4]. First, these neurohormonal pathways increase both pre- and afterload and cause cardiotoxicity, myocyte hypertrophy/death, and changes in arterial compliance. Second, they progressively turn on other detrimental systems; these include an imbalance between the generation of reactive oxygen species (ROS) and antioxidative enzymes, as well as pro-inflammatory changes. Gradually, peripheral maladaptations occur. For the symptomatic and exercise intolerant CHF patient, endothelial dysfunction, skeletal muscle wasting and ventilatory inefficiency play a key role [5,6] (Fig. 1). Indeed, it has long been recognized that poor cardiac performance is not the sole reason for impaired exercise tolerance [7]. Resting left ventricular ejection fraction correlates poorly to exercise capacity in CHF patients [8]. The lack of rapid clinical improvement following cardiac transplantation also argues for other than pure cardiologic or hemodynamic determinants [9].

Impaired endothelium-dependent vasodilation reduces myocardial perfusion and increases ventricular afterload. As such, the stage is set for a negative spiral, which eventually results in progressive cardiac dysfunction. Lack of an adequate vasodilatory response to exercise hampers blood flow to working peripheral muscles and further limits physical performance. Training improves systemic endothelium-dependent vasodilation in CHF patients [10], which correlates well with the achieved gains in peak aerobic capacity. Moreover, by decreasing peripheral vascular resistance and ventricular afterload, cardiac performance is facilitated [11].

At the cellular level, endothelial dysfunction reflects a decreased bioavailability of nitric oxide (NO) and results from an imbalance between endothelial damage and repair. Activation of the above-mentioned neurohormonal systems, the generation of ROS [12] and a typical pro-inflammatory milieu [13] are not adequately counterbalanced by local and bone marrow-derived endothelial restoration [14]. As such, the basic concept of endothelial dysfunction has shifted from a pure "damage model" to a more dynamic process in which endothelial repair fails to keep pace with local injury.

In the following, we will focus on recent progress with regard to endothelial dysfunction in CHF patients and how exercise training modulates physical performance of this patient group through endothelial repair mechanisms.

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0167-5273/$ – see front matter 
doi:10.1016/j.ijcard.2012.04.106

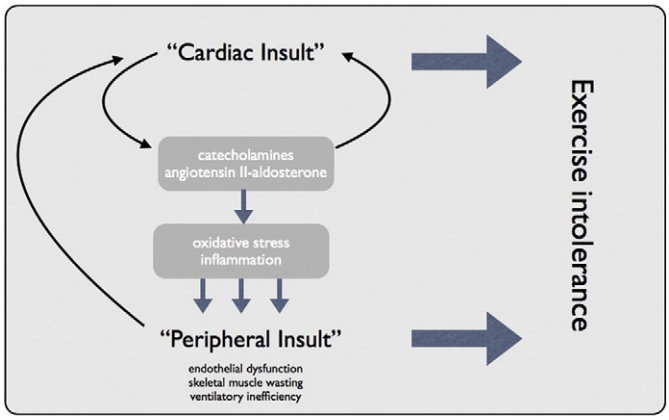


**Fig. 1.** Determinants of exercise intolerance in patients with (CHF). A cardiac event activates neurohormonal systems, leading to peripheral maladaptive processes such as endothelial dysfunction, skeletal muscle changes and ventilatory inefficiency. With progression of CHF, peripheral changes become at least equally important as the central hemodynamic factors in limiting exercise capacity.

## 2. Cellular mechanisms for endothelial repair

Fifteen years ago, it became evident that endothelial repair does not solely depend on the proliferation of mature endothelial cells [15], but also on the mobilization and functional capacity of bone marrow-derived endothelial progenitor cells (EPC) [16]. In contrast to mature endothelial cells, which are limited in their proliferative capacity, EPC are highly proliferative cells with an endothelial phenotype *in vitro* and forming spontaneous blood vessels *in vivo* [17,18]. EPC (also called endothelial colony forming cells or late outgrowth EPC) are derived from adherent peripheral blood mononuclear cells (PBMC), cultured in an endothelial medium for 6–21 days. Colonies from these cells display a cobblestone morphology [19]. Because of the membrane expression of progenitor (CD34) and endothelial (KDR) markers, flow cytometry has become a strong tool in the enumeration of EPC, which circulate in peripheral blood in very low quantities. Accumulating evidence has demonstrated that CD34+/KDR+ progenitor cells not only appear to play an important role in re-endothelialization [20] and neovascularization [21], but also serve as predictive biomarkers for several cardiovascular diseases [22]. To date, numerous studies have been published on pharmacological and non-pharmacological approaches, including exercise training, that aim to increase EPC numbers and function [23–26].

In response to endothelial injury, EPC are mobilized from the bone marrow, a process that first requires activation of matrix metalloproteinase (MMP)-9. Subsequent cleavage of membrane-bound Kit ligand (mKitL) and binding of sKitL to its receptor on stem/progenitor cells (cKit) will allow these cells to migrate to the vascular zone of the bone marrow. Angiogenic factors, such as vascular endothelial growth factor (VEGF) and stromal derived factor (SDF)-1α, expressed by hypoxic tissues, subsequently direct homing of EPC to the damaged vascular wall through binding on their receptors (VEGFR2/KDR and CXCR4 respectively) (Fig. 2).

Searching for the true identity of EPC led to the identification of another cell type, known to contribute to the maintenance of an intact endothelial cell layer. Circulating angiogenic cells (CAC) appear after 4–7 days of culture of PBMC in an endothelial cell medium. Recently, progress has been made in unraveling the true nature of CAC. From genotypic, proteomic and immunophenotypic analyses, the monocytic nature of CAC could be established [27]. More specifically, it has been shown using transcriptome analysis, that the CAC gene signature is highly enriched for markers of M2 macrophages, whereas expression of M1 macrophage markers is low [28]. Pro-angiogenic genes are also highly expressed on CAC and they display a high phagocytic index. Despite the resemblance to M2 macrophages, their role in angiogenesis is confirmed and has been linked to the paracrine release of angiogenic cytokines, with an essential role for IL-8 [28].

In contrast to late outgrowth EPC, short-term cultured CAC have limited proliferative capacity and do not form vascular networks [29]. Several investigators have studied the role of CAC in re-endothelialization and neo-vascularization. In animal models of denudation of the carotid artery, transfusion of cultured CAC at the site of injury led to enhanced re-endothelialization, compared to EPC alone [30]. As such, EPC and CAC have synergistic functions in the process of endothelial repair [31].

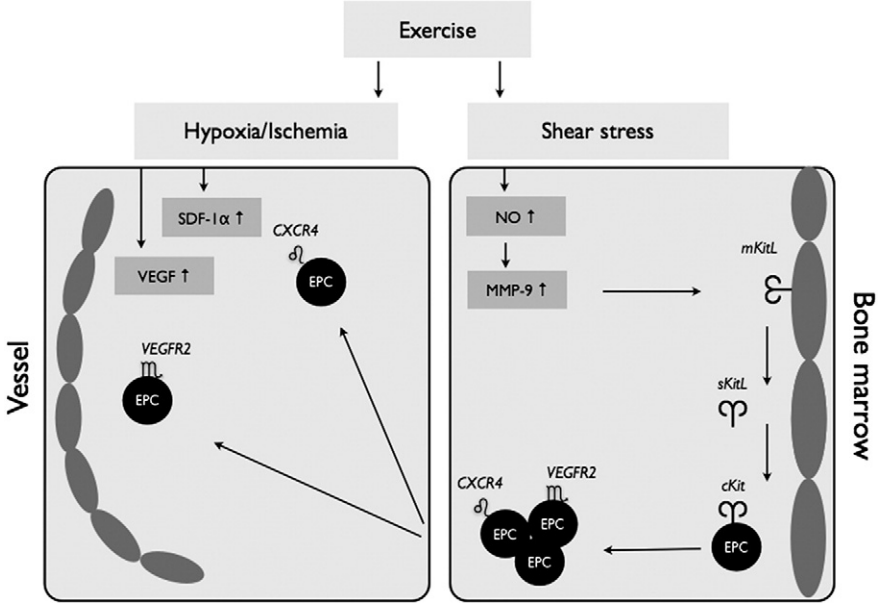


**Fig. 2.** Schematic drawing of the processes that account for the effects of exercise training on the regenerative capacity of EPC.Through enhanced shear stress, endothelial nitric oxide synthase (eNOS) is upregulated. Increased NO production leads to activation of matrix metalloproteinase (MMP)-9, which cleaves membrane bound Kit ligand (mKitL). The latter binds to cKit receptors on EPC, thereby allowing these cells to migrate to the vascular zone of the bone marrow. Angiogenic factors, such as vascular endothelial growth factor (VEGF) and stromal derived factor (SDF)-1α, expressed by hypoxic tissues, subsequently direct homing of EPC to the damaged vascular wall.