



Opinion

The Impact of Endothelial Progenitor Cell Dysfunction in Heart Failure “Obesity Paradox”

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Keywords

Cardiac failure; Obesity; Endothelial progenitor cells; Endothelial function; Vascular reparation

Introduction

Heart failure (HF) is a major factor in premature death and inability in the patient with established cardiovascular (CV) disease worldwide [1]. Although CV diseases mediate half of the cases of all newly diagnosed HF, diabetes mellitus and other metabolic diseases may sufficiently increase a risk of HF development and progression [2]. On the other hand overweight and obesity strongly associating with the exaggerated level of the CV risk among none-HF individuals do not relate to poor clinical outcomes in HF patients [3,4]. This phenomenon determines the “obesity paradox”, which is being a U-shaped association between body mass index (BMI) and long-term prognosis in HF patients [5,6]. Interestingly, this paradox has found in many people of the HF patients without corresponding to the number of conventional CV risk factors [7]. Although several explanations of causes of “obesity paradox” development are discovered, most studies appear to be limited by the daily use of BMI to classify the severity of obesity [8]. Indeed, standard anthropometric measures of body mass adjusted to height square, hip and waist circumstances with a further calculation of hip-to-waist ratio that appears to be useful for grading overweight, underweight and obesity have implemented into routine clinical practice to easily stratify the patients from the general population. However, dual-energy X-ray absorptiometry-based obesity criterion, which is recognized as a gold standard to determine body fat deposition, better approximates the percentage of body fat in individuals with BMI value ≥ 25 kg/m². Consequently, despite the measure of BMI alone has been considered an inaccurate marker of labelling obesity, there is evidence regarding being of both the non-obese and the morbidly obese individuals had a significantly higher risk of all-cause mortality and HF-related clinical outcomes compared with the obese group 3. Thus, long-term prognosis may not be relevant in HF patients with morbid obesity and, however, traditional CV risk factors do not completely contribute to the “obesity paradox”. The fact regarding that the “obesity paradox” does not fully extend to HF symptoms, and that CV risk factors including

age and gender may not correspond to “obesity paradox” appears to be intriguing [9].

There are numerous clinical trials and meta-analysis that have strongly documented a significant difference between overweight / obese HF patients and normal BMI/underweight HF individuals in a risk of all-cause mortality rate and CV mortality rate. Indeed, lowered BMI or percent body fat in HF individuals related closely to worse clinical outcomes when compared to overweight/obese HF patients [10-12]. On the other side, the role of the transformation of metabolically healthy obesity to metabolically non-healthy obesity in development and progression of HF and worsening clinical outcomes is under fire and require more investigations.

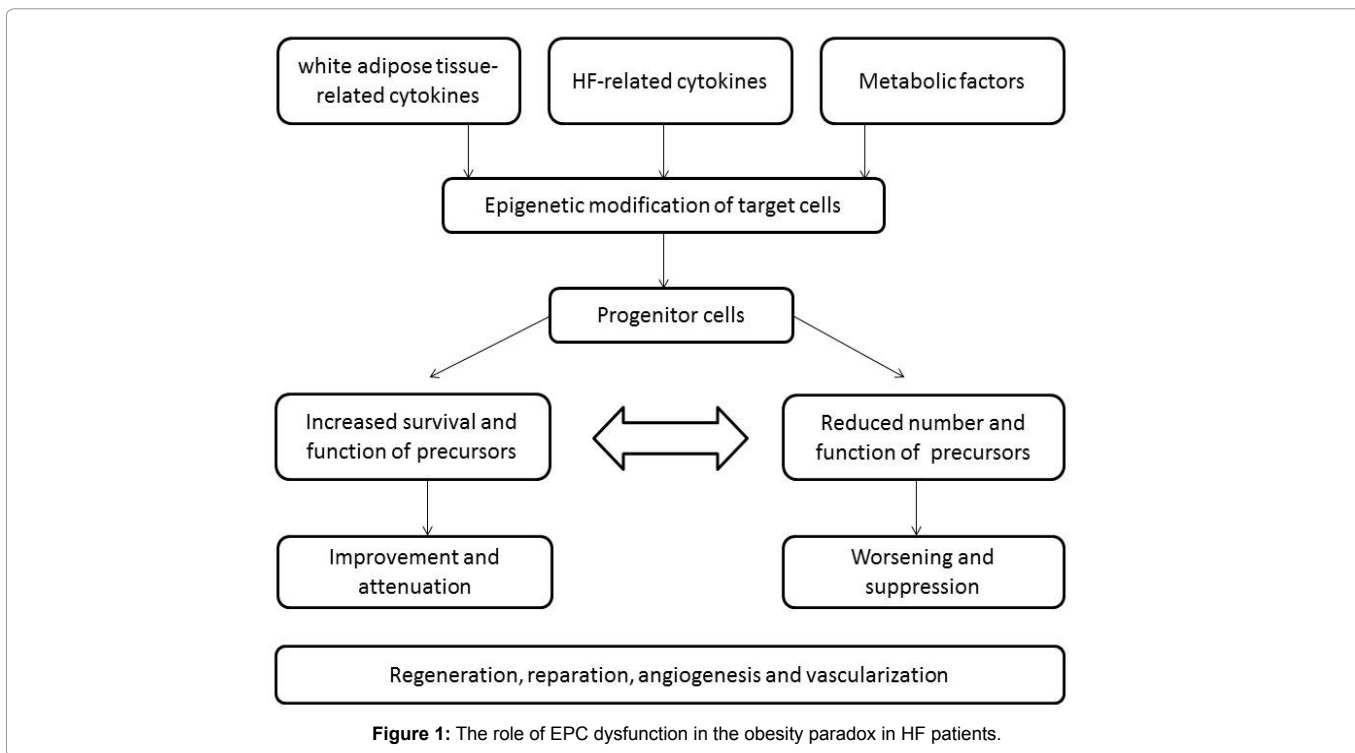
Although innate molecular mechanisms of “obesity paradox” in HF population are not fully completed, it has been suggested that adipocytokine dysfunction may be a key underlying factor contributing in natural evolution of both diseases (abdominal obesity and HF) [10]. Recent preclinical, clinical and observational studies have shown that white adipose tissue (WAT) cells especially allocated around the heart and along adventitia of blood vessels produce and release into circulation the wide range of adipocytokines (leptin, apelin, progranulin, chemerin, tumour necrosis factor-alpha, visfatin and vaspin), which provide direct and indirect effects on cardiac and vascular remodeling / function, as well as on CV system totally [13-17].

Previous studies have demonstrated that WAT-related pro-inflammatory cytokines (tumor necrosis factor-alpha, visfatin and probably vaspin) are able to suppress the intracellular free calcium input, cell membrane enzymes and ionic channels and SERCA- co-regulators, and thereby to impair cardiac systolic function [15,16]. Therefore, they may induce oxidative stress and inhibit autophagy ability of cells that leads to the weak function of the main component of vascular repair system - endothelial progenitor cells (EPCs) [15-19]. In opposite, supporting of endothelial function and vascular reparation associates with synthesis and secretion of other WAT-related cytokines, i.e. adiponectin and omentin. The circulating levels of both in peripheral blood in individuals with obesity are significantly decreased [20]. The number of capillaries depends on intensity of both angiogenesis / neovascularization and destroying of capillary walls and is critical for mediating metabolic supply of peripheral tissue. In this context, functional activity and survival of EPCs that involves in the vascular regeneration of target organs play a pivotal role in restoring impaired structure and function of them [21,22]. Along consequent pathophysiological stages of HF nature evolution, WAT dysfunction interplays in cardiac and vascular remodeling, tissue insulin resistance and peripheral tissue metabolism regulation, as well as directly cooperates with mobbing, differentiation and proliferation of EPCs.

Although there are numerous preclinical and clinical trials, which have confirmed the importance of impaired obesity-related metabolomics in HF in altered myocardial contractility function, apoptosis and fibrosis in the heart and accelerating atherosclerosis [23], the causative role of EPC dysfunction in the development of “obesity paradox” in HF is under fire and requires more investigations [24,25].

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Received: November 29, 2017 Accepted: December 14, 2017 Published: January 10, 2018



Despite a lack of uniform definition of EPCs they have been frequently defined as CD45dim precursor cells with cumulative expression of both hematopoietic stem cells (CD34) antigen and endothelial cell antigens (CD309, CD133, CD31) [26]. Depending on the predominant ability of EPCs to shape of colonies in vitro there are early and late outgrowth populations of progenitor cells. Late outgrowth subpopulation demonstrates a protective impact on the vasculature supports endothelial function and promotes neoangiogenesis and vascularization [27]. Early-outgrowth subpopulation exhibited less protective effects on late-outgrowth EPCs. Additionally, the potency of EPCs to migration, proliferation, differentiation, adhesion, and mobbing of EPCs are under tight control of autocrine/paracrine mechanisms and epigenetic regulation [28]. Indeed, the functionality of late outgrowth EPCs is regulated by not only WAT cytokines, but increased size/volume of adipocytes of WAT. It is well known that the number of circulating EPCs in metabolically healthy obese individuals with HF is increased to healthy volunteers, while the development of metabolically non-healthy or morbid obesity in HF strongly associated with EPCs dysfunction [29].

The exact innate molecular mechanism by which the EPC function may differ in metabolically healthy vs non-healthy obese patients is not completely clear. Probably, some epigenetic stimuli contributing in the modification of secretome actively released by precursors could be taken into consideration as an initial factor for EPC dysfunction. The secretome definition is widely considered a collection of numerous molecules secreted by cells into the extracellular space with several ways as directly and indirectly via shaping of micro vesicles and nanoparticles. There is a large body of evidence regarding that several potencies of EPCs are regulated by the signals transferred through secretome releasing from other cells including antigen-presenting cells, endothelial cells and even adipocytes [20]. Additionally, the ability of endothelial cells and EPCs to secretome

releasing could be impaired due to ischemia, hypoxia, inflammation, endotoxemia, non-specific cell activation, and coagulation [22] that leads to endothelial dysfunction and presentation of CV diseases including HF [23,24]. Because secretome is not only cargo for some molecular components, but it is also the main factor for cell-to-cell cooperation, there is suggested that epigenetic modification could be a very early and initiating stimuli for shaping precursor dysfunction. However, the phenomenon called metabolic memory that associates with diabetes mellitus are mediated by secretome modification [30,31]. Whether this effect would be essential for EPC dysfunction in obesity beyond diabetes mellitus is not understood, while this is highly probably [29]. A role of several factors in EPC dysfunction is reported in Figure 1.

Conclusion

In conclusion, the “obesity paradox” is the result of interference between repair system triggers and a wide range of pathophysiological factors contributing to the damage of target organs (heart, vessels, kidney, WAT, muscles, etc.). The EPCs are in the focus of this cooperation and development of EPC dysfunction could explain several controversies in the pathogenesis of HF. Large clinical trials are required to accurately evaluate the possible link between obesity and EPCs dysfunction in HF to clearly understand these multiple complex relationships.

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