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"Obesity Paradox" in Heart Failure: The Possible Role of Progenitor Endothelial Cell Dysfunction

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Abstract

The "obesity paradox" phenomenon is referred to as a U-shaped curve between long-term prognosis and body mass index in heart failure patients. There is a large body of evidence regarding the regulatory role of visceral adipose tissue-related adipocytokines in activity of endogenous repair system. The reparation of myocardium and endothelium may strongly enhance by differentiation and mobbing of endothelial progenitor cells (EPCs). They improve angiogenesis and collateral vessel growth, as well as counteract vascular injury. It has suggested that several metabolic factors frequently associated with HF may increase the number of circulating EPCs, which mediate repair processes and collaborate with obese. In contrast, decreased number and/or weak functionality of EPCs relate with altered endogenous repair system and may negatively contribute in HF development. Finally, moving across recently received evidence "obesity paradox" could be elucidated as a result of interplaying of trigging repair systems and ability of EPCs to response on challenges enhancing reparative potency in target organs, i.e. myocardium, vascular wall and endothelium.

Keywords: Heart failure; Obesity; Progenitor cells; Reparation

Heart failure (HF) is a leading cause of the death and inability amongst patient with known cardiovascular (CV) disease [1]. It is well known that some metabolic diseases, i.e. overweight, abdominal obesity and diabetes mellitus, may lead to increased risk of newly diagnosed HF [2]. Although overweight and obese patients have a higher risk of CV events and disease in general population, in case of chronic HF and acutely decompensated chronic HF they also exhibit more favorable clinical outcomes in long-term perspective in comparison to normal body weight individuals [3,4]. This phenomenon is now referred to as the "obesity paradox" [5] and it depicts a U-shaped curve between long-term prognosis and body mass index (BMI) in HF patients [6]. Interestingly, this paradox has established in several populations of the HF patients corresponding to CV risk factors in abundant [7]. Nevertheless, numerous studies and meta-analysis have strongly documented an obesity paradox, in which overweight and obese patients, defined by body mass index, percent body fat, or central obesity, demonstrate that the risk for total mortality and CV mortality and admission rate was highest in chronic HF patients who were underweight as defined by low BMI, whereas risk for CV mortality and hospitalization was lowest in overweight and obese subjects [7-10].

The molecular mechanisms developing of "obesity paradox" in HF population are still uncertain, while adipocytokine dysfunction is reported as key factor, which contributes in pathogenesis of both settings, i.e. obesity and HF. However, the proinflammatory effect of overexpression of adipocitokines and their receptors in peripheral tissues in HF individual do not completely explain the favorable impact of obese on survival.

It has suggested that some adipocytokines produced by white adipose tissue (WAT) especially allocated around heart and blood vessels might mediate controversial effects on CV system [11,12]. The broad spectrum of VAT-related cytokines, which exhibit an exaggerated merge in obese (i.e., leptin, apelin, progranulin, chemerin, tumour necrosis factor-alpha, visfatin and vaspin), may depress the intracellular free calcium input, suppress myocardial systolic function and induce weak endothelial progenitor cells through increasing oxidative stress and inhibiting autophagy ability [13-17]. In contrast, in obesity relatively deficiency of adiponectin and omentin, which are able to attenuate reparative effects of peripheral tissues including myocardium and endothelium, was found [18]. As a result, the activity of progenitor cells involving in regeneration of damaged myocardium and impaired endothelium, improvement of metabolism of target cells, angioneogenesis and neovascularization, is dramatically increased [19,20]. By now, endothelial progenitor cells are considered as a much more promised factor coordinating proinflammatory VAT dysfunction in obese and cardiac/vascular remodeling in HF as well as interplaying in other mechanisms of HF progression, i.e., neurohumoral activation, metabolomics impairment and altered reparative capability.

Although numerous preclinical and clinical trials have already established the important role of impaired obesity-related metabolomics in HF patients in predicting myocardial contractile dysfunction, mediating apoptosis and fibrosis in the heart and vessels, as well as anti-inflammatory and anti-atheromatous effects in peripheral tissues [21], the causative role of progenitor cells dysfunction in "obesity paradox" in HF is now under intensive investigation [22,23].

By now, EPCs have defined as cells, which are positively labeled with both hematopoietic stem cells (CD34) and endothelial cell markers, i.e., predominantly vascular endothelial growth factor receptor-2, CD31 cumulatively [24]. There are at least two phenotypes of progenitors, i.e., early outgrowth and late outgrowth cells exhibiting different effects on target cells and distinguishing one another in functionality, i.e., endothelial colony forming ability. Late outgrowth EPCs as a subpopulation of progenitors exhibit a protective impact on the endothelium mediating proliferation and having the ability to promote angiogenesis and collateral vessel growth [25]. These processes are under closely autocrine/paracrine and epigenetic regulation affected in particularly migration, proliferation, and mobilization of EPCs from bone marrow and peripheral tissues [26].

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Increased adipocyte size is hypothesized to signal the recruitment of late outgrowth EPCs. In metabolically healthy obese individuals with HF the number of EPCs in the circulation is frequently increased or near normal. In contrast, development of metabolically non-healthy obese associates with HF there is a reduced ability of EPCs to realize their potency in proliferation, differentiation, adhesion, migration, incorporation into tubular structures, and survival is now defined as EPC dysfunction [27]. The weak EPCs functionality may associate with lowering EPCs' count in the peripheral blood that is considered an initiation of endothelial dysfunction, which is independent factor contributing in CV events and disease [28]. In contrast, some metabolomics components in obese are able to stimulate differentiation and mobbing of EPCS, as well as support their functionality to restore structure and function of damaged endothelium.

Consequently, "obesity paradox" in HF individuals might relate to EPCs dysfunction, the final integrative effect of which depends on CV risk factor presentation, imbalanced number of circulating level of early/late outgrowth EPCs contributing in reparative processes, and weak functionality of EPCs. Shaping impaired pattern of circulating EPCs with lower functionality may predict mortality rate in HF population. In contrast, increased circulating number of EPCs at early stages of HF development in obese patients may create advantages in survival due to well controlled repair ability of endothelium and probably impaired myocardium.

Conclusion

In conclusion, "obesity paradox" is probably result of interplaying of trigging repair systems and ability of EPCs to response on challenges enhancing reparative potency in target organs, i.e., myocardium, VAT, vascular wall and endothelium. More clinical studies are required to pretty accurately evaluate the link between obesity and HF and help us to understand more fully this multiple complex relationships.

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