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C-Type of Natriuretic Peptide and Progenitor Endothelial Cell Dysfunction: The Link to Heart Failure Development

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Abstract

C-type of natriuretic peptide (CNP) is a promising biomarker of heart failure (HF) development and HF-related clinical outcomes. Recent clinical studies have shown that elevated level of CNP strongly related to cardiac hemodynamic overload, myocardial ischemic injury, endothelial dysfunction, early atherosclerorsis, and worsening vascular repair. Whether CNP plays a regulatory role in restoring endothelium structure and function through modulating repair capacity of endothelial progenitor cells (EPCs) is not fully clear. However, CNP counteracts angiotensin II, which mediates NF-kappaB-dependent pro-inflammatory genes, peroxisome proliferator-activated receptor-α and –γ genes, NADPH/NADH oxidase genes in EPCs, deficiency of which is considered a marker of HF development and advance. The aim of the short comment is to discuss the role of CNP as mediator of vascular reparation and a marker of restoring of endothelial function in HF patients.

Keywords: Heart failure; C-type of natriuretic peptide; Progenitor endothelial cell; Biomarkers

C-type of Natriuretic Peptide in Heart Failure

C-type natriuretic peptide (CNP) is a paracrine growth factor, which is mainly expressed in the central nervous system, bone and vasculature and belongs to the family of natriuretic peptides [1]. CNP is secreted predominantly from vascular endothelial cells and rarely in myocardium and involved in a variety of homeostatic processes including regulation of vascular tone, vascular remodeling, and endothelial regeneration acting via smooth muscle guanylyl cyclase-B (GC-B) and specific receptor (NPR-B) [2]. Additionally, there are two matter forms of CNP: tissue-associated CNP-53 and circulating CNP-22, for which the gene transcription is located on chromosome 2 and is regulated by similar triggers, i.e., pro-inflammatory cytokines (tumor necrosis factor and interleukin-1), transforming growth factor-beta, hypoxia-inducible factor, mechanical stretching, ischemia [3-5]. Indeed, circulating CNP level strongly related to cardiac hemodynamic load and ischemic injury [6]. Interestingly endothelium-derived CNP is involved in the regulation of vascular tone, remodeling, and vascular repair independently of vascular smooth muscle GC-B [7].

According methodological point of view an amino-terminal fragment of CNP (NT-proCNP) assay demonstrated more pretty accurately consistent and reliable data than CNP and may be preferred for usage in several clinical settings including heart failure (HF) [8].

Discussion

Although there is a traditional view of CNP as an endothelial-related peptide, contemporary studies published in recent years has exhibited new evidence regarding the role of CNP in contribution to cardiovascular function especially regulating cardiac hypertrophy and cardiovascular remodeling. There is large body of evidence that circulating levels of mainly amino-terminal fragment of CNP (NT-proCNP) and rarely CNP positively associated with arterial stiffness, endothelial dysfunction, cardiac failure, pulmonary hypertension and early atherosclerosis [9-12]. Formerly it has established that CNP and NT-proCNP were significantly increased in acute, acutely decompensated and chronic HF and they were significantly correlated to NYHA classification and echocardiographic-derived features of myocardial structure and function [13,14]. Later it has been become to know that NT-proCNP could be a strong independent marker for clinical outcome including death, admission/readmission in patients with known HF with preserved left ventricular ejection fraction (HFpEF), but not in those with HF with reduced left ventricular ejection fraction (HFrEF) [15]. Moreover, NT-proCNP is not only significantly elevated in critically ill patients, but strongly associated with long-term outcome in this population [16].

However, the CNP may play a pivotal role in restoring endothelium structure and function through modulating repair capacity of endothelial progenitors, deficiency of which is considered a marker of HF development and advance [17-19]. Recently it has suggested that various functions of endothelial progenitor cells (EPCs) such as ability to proliferation, migration, colony shaping and differentiation, by which an

endothelium repair and angiogenesis are realized, may be under autocrine/paracrine control by CNP. Indeed, CNP is functional antagonist of angiotensin II, which mediated NF-kappaB-dependent pro-inflammatory genes, peroxisome proliferator-activated receptor-α and –γ genes, NADPH/NADH oxidase genes in EPCs [20-22]. Therefore, angiotensin II is powerful co-stimulator of transcription of several active molecules, i.e., monocyte chemotactic protein-1, macrophage-colony stimulating factor, endothelial-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, inducible nitric oxide synthase, and cyclooxygenase-2 [20]. All these factors are involved in contribution of shaping EPC dysfunction associated with weak of their functionality and lowering their number in peripheral blood [23]. On the other hand, increased circulating level of CNP is considered an adaptive response to overcome of EPC resistance and improving vascular reparation [24,25]. Whether CNP is a marker of EPC dysfunction or it is factor contributing in development and progression of vascular injury and endothelial dysfunction in HF is not completely clear. Probably monitoring of CNP concentration in HF individuals could improve at risk stratification, when cardiovascular risk factors, i.e., diabetes, hypertension, kidney disease, obstructive pulmonary disease, are presented. Moreover, it has postulated that increased level of CNP reflecting a stretch of adaptive mechanisms of vascular reparation may predict a higher risk of HF in general population of individuals.

Conclusion

CNP is considered a biomarker of HF outcomes and probably other HF-related events including readmission. Future large clinical trials are required to more pretty accurately explain whether exaggerated production of CNP is adaptive response to improve reparation of vascular endothelium. The predictive value of elevated CNP in HF individuals is probably needed to confirmation.

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