Can Adiponectin be a Novel Metabolic Biomarker for Heart Failure?

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Recently, adipokines have been reported as involved in obesity-associated diseases, such as hyperlipidemia, type 2 diabetes mellitus, insulin resistance, hypertension, ischemic heart disease and heart failure. Among those, adiponectin, a 30-kDa polypeptide hormone secreted from adipocytes, is an anti-diabetic, anti-atherogenic and cardioprotective protein, concentrations of which are decreased in vascular disorders. However, in patients with chronic heart failure (CHF), several prospective studies have revealed that adiponectin levels correlate with the plasma levels of B-type natriuretic peptide (BNP) and cytokines such as tumor necrosis factor (TNF)-α, and that high levels of adiponectin are associated with severity and increased mortality.

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Why are adiponectin levels much higher in patients with CHF? Low adiponectin levels have been observed in patients with left ventricular hypertrophy, successful reperfusion after acute myocardial infarction and acute coronary syndrome. Considering the cardioprotective effect of adiponectin, the compensatory response would be a pathophysiological mechanism, much like the natriuretic peptide system. However, the significance and mechanisms for higher levels of adiponectin in CHF remains controversial. In contrast, it has been demonstrated that circulating adiponectin was not associated with incident CHF in a community-based asymptomatic cohort of men and in the Framingham Offspring Study. It is not fully understood whether increases in adiponectin levels persist throughout the entire course of cardiac dysfunction, or whether higher levels are a transient compensatory mechanism to protect the impaired myocardium. Moreover, it is postulated that localized production of adiponectin in coronary microvascular endothelium affects blood flow distribution and myocardial tissue metabolism. Thus, further research is needed to evaluate the influence of changes in both plasma and tissue levels of adiponectin in the pathophysiology of CHF.

Can adiponectin be used as a metabolic biomarker to predict the outcome in patients with CHF? Can the treatment regimen for heart failure modulate the adiponectin levels? In this issue of the Journal, Yamaji et al examine the effect of a β-blocker, carvedilol, on plasma adiponectin levels in patients with CHF. They found that plasma adiponectin, BNP and norepinephrine levels decrease concomitantly with an increase in left ventricular ejection fraction (EF) 6 months after treatment with carvedilol. Further, they defined the patients in whom EF increased more than 4% within 6 months of carvedilol treatment as responders; 50% of patients were responders, and the responders showed a greater decrease in adiponectin levels than in both norepinephrine and BNP levels. They also found that changes in adiponectin were more positively correlated with body mass index than with BNP. Thus, the authors conclude that carvedilol decreases plasma adiponectin levels and that the decrease in plasma adiponectin level may contribute to the improvement of EF observed after treatment with carvedilol in CHF patients. Although several limitations are noted in the interpretation of the results, these findings suggest that not only neurohumoral or hemodynamic, but also metabolic abnormalities contribute to the increased plasma adiponectin levels in CHF and that chronic treatment with carvedilol improves these abnormalities in patients with CHF. Unfortunately, they have not examined the metabolic effect on the decrease in adiponectin and the cardiac remodeling process by carvedilol. Carvedilol has an anti-oxidant action, which might cause an improvement in cardiac dysfunction. How does a decrease in plasma adiponectin by treatment with carvedilol contribute to the improvement of LVEF? Is it paradoxical?

CHF is characterized by impaired ventricular function and neurohumoral activation, including the inflammatory process, which is accompanied by an excess of oxidative stress. Oxidative stress contributes to myocyte apoptosis, has direct negative inotropic effects, and reduces the bioavailability of nitric oxide (NO), leading to impaired vasodilation of the coronary, pulmonary and peripheral vascular beds. Adiponectin binds to endothelial cells and enhances NO production and thus causes myocardial fibrosis and reduced capillary density after coronary injury. Adiponectin interferes with macrophage function, leading to the suppression of interleukin (IL)-6 and TNF-α production and induces the production of anti-inflammatory factors, such as IL-10 and IL-1R. On the other hand, a lack of adiponectin reduces NO production and thus causes myocardial damage in ischemia–reperfusion models. Shibata et al have reported that adiponectin knockout mice show exacerbated left ventricular dilation, myocyte hypertrophy and systolic dysfunction concomitant with myocyte apoptosis, interstitial fibrosis and reduced capillary density after coronary ligation. Administration of adenovirus-mediated adiponectin reverses those changes. Adiponectin promotes cell survival and inhibits cell death, which suggests that adiponectin may directly protect cardiomyocytes, in addition to its
Adiponectin in HF

**Figure.** Heart failure: metabolic, immune and inflammatory response. EF, ejection fraction; NO, nitric oxide.

vascular actions. Thus, adiponectin may exhibit a cardio-protective action through suppression of cardiac remodeling as shown in Figure. The favorable effects of adiponectin seem similar to the therapeutic and diagnostic strategies of natriuretic peptides.

Potential markers of CHF include neurohormonal mediators, markers of myocyte injury, and indicators of systemic inflammation. Among these, BNP and NT-pro-BNP are the most widely studied and appear to be the most useful for risk assessment of patients with CHF. BNP mainly reflects hemodynamic overload, so it has been established as a biomarker of the severity of CHF.

Does adiponectin also reflect hemodynamic overload? How does adiponectin directly cause an increase in EF? Adiponectin modulates a number of metabolic processes, including glucose regulation, fatty acid catabolism and insulin resistance. Thus, it is postulated that adiponectin is a metabolic, and BNP a hemodynamic, biomarker in patients with CHF.

Recent randomized clinical trials have demonstrated that the β-blockers, especially carvedilol, reduce the mortality associated with CHF. Nevertheless the magnitude of the clinical benefit, the exact mechanism of action have not been elucidated. Sympathetically mediated effects resulting in calcium overload within myocardial cells would contribute to myocyte necrosis, to direct activation of apoptotic pathways, and have direct effects on myocardial hypertrophy and fibrosis. The interplay and interactions with other neurohumoral factors, cytokines and cell-signalling pathways remain to be fully determined. Adiponectin may participate in the beneficial process of β-blockers in CHF. Therefore, it is important to examine the adiponectin and related mechanisms responsible for CHF and the effect of β-blockers.

**References**