Carperitide and Adiponectin
—— How Are They Connected Each Other to Benefit Acute Decompensated Heart Failure? ——

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ANP and Heart Failure
The heart has been thought to be merely a pump to collect and circulate blood to and from the heart. However, this is not the case as several investigators have noticed the existence of granules in atrial muscle cells, suggesting that the atrial muscle may produce certain substances. After many years, Matsuo and Kangawa discovered that one of the substances is human atrial natriuretic peptide (ANP, carperitide). This observation opened a new era for cardiology because we noticed that the heart is the secretary organ that controls hemodynamics.

Heart Failure and Metabolic Disorder
CHF is primarily characterized by impaired cardiac performance; however, recent accumulated evidence strongly indicates that neurohumoral imbalance, inflammation and metabolic abnormalities contribute to high mortality. Intriguingly, increases in plasma catecholamine and angiotensin II levels are thought to play important roles in the pathophysiology of CHF; and they both culminate in abnormal glucose tolerance. Either transient high glucose exposure or decreased insulin sensitivity, which are known to be major cardiovascular risk factors, can result in cellular injury via the generation of oxidative stress and provocation of myocardial apoptosis.

In contrast, plasma adiponectin levels are reported to be negatively correlated to insulin resistance. Adiponectin is one of the circulating adipocytokines, and it plays an important role in energy homeostasis, regulating insulin sensitivity, lipid metabolism and exerts anti-inflammatory properties. Adiponectin knock-out mice develop severe cardiac hypertrophy and exhibit increased mortality subjected to pressure overload caused by transverse aortic constriction. Conversely, adenovirus-mediated overexpression of adiponectin attenuates cardiac hypertrophy following pressure overload in adiponectin knock-out mice. Therefore, adiponectin and carperitide are also thought to contribute to the pathophysiology of CHF.

ANP and Adiponectin in Patients With CHF
The authors of previous studies have found that carperitide infusion increases plasma adiponectin levels in patients with acute decompensated heart failure (ADHF). However, the effect of carperitide on plasma adiponectin levels in patients with diabetes mellitus (DM) remains unknown.

In this issue of the journal, Yamaji et al evaluated the effect of carperitide on plasma adiponectin levels in ADHF patients with or without DM. They clearly demonstrated that plasma adiponectin levels significantly increased with an increase in ANP and a decrease in BNP 7 days after carperitide infusion. Furthermore, they demonstrated that the adiponectin levels before the proper treatment were slightly lower in ADHF patients with DM, and that the percentage increase in adiponectin levels was significantly greater in ADHF patients with DM than in those without DM. They also demonstrated that both higher plasma aldosterone levels and prevalence of DM were significant independent predictors of a greater percentage increase in adiponectin levels after treatment with carperitide.

Several studies have suggested a positive correlation between plasma levels of ANP and/or BNP and adiponectin in patients with CHF. Therefore, high levels of plasma adiponectin are associated with increased mortality and severity in patients with CHF.

How are both carperitide and adiponectin connected to each other? It has been proposed that cardiac natriuretic peptides have a novel lipolytic and potential lipid-mobilization effect that is mediated by a GC-A receptor. Tsukamoto et al demonstrated that normal (10⁻¹⁰ mol/L), pathophysiologic (10⁻¹⁰ mol/L) and pharmacological (10⁻⁹ mol/L) concentrations of ANP enhanced adiponectin mRNA expression and increased adiponectin secretion via the GC-A/cGMP/PKG-dependent pathway by primary cultured human adipocytes. This indicates that carperitide can affect adipose tissues and increase adiponectin production; however, it is not the case vice versa (Dr Tsukamoto, personal communication).

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.
How Does Adiponectin Exert the Cardioprotective Effect Under Stress Conditions?

Shibata et al demonstrated that adiponectin activates AMP-activated protein kinase (AMPK), and inhibits the hypertrophic response to α-adrenergic receptor stimulation. Furthermore, AMPK is activated by ischemia–reperfusion, as well as in hearts with pressure overload hypertrophy and subsequent heart failure. AMPK is expressed in various tissues, including the myocardium, and plays a central role in the regulation of energy metabolism under stress conditions.

Interestingly, Eurich et al reported the results of a meta-analysis showing that metformin was the only anti-diabetic agent to reduce all-cause mortality without causing any harm in patients who had heart failure and DM. Metformin is known to activate AMPK similar to adiponectin. Recently, Sasaki et al demonstrated that long-term oral administration of metformin decreases apoptosis, inhibits cardiac remodeling and prevents the progression of heart failure in a rapid pacing-induced heart failure dog model, which is considered to be similar to human dilated cardiomyopathy, along with increases in AMPK activation. Furthermore, AICAR, another AMPK activator, had effects almost equivalent to those of metformin, suggesting that AMPK activation plays a primary role in reducing apoptosis and preventing heart failure.

What Mechanisms Following AMPK Activation Are Involved in Cardioprotection?

The first possibility is enhancement of nitric oxide (NO) production. CHF is characterized by impaired cardiac performance, neurohormonal imbalance, inflammation and metabolic abnormalities including abnormal glucose tolerance, which is accompanied by an excess of oxidative stress. The excess of oxidative stress causes the impairments of endothelial cells attached to cardiomyocytes, and the endothelial dysfunction may be involved in the deterioration of CHF. AMPK is known to phosphorylates eNOS, resulting in an increase in NO production, and thus inhibits inflammatory cytokine-induced expression of cell adhesion molecules, and suppresses oxidative stress.

The second possibility is related to the improvement of insulin resistance and metabolic abnormalities. Under normal conditions, the adult heart utilizes predominantly fatty acids to derive the majority of its energy. However, metabolic remodeling such as a marked shift in substrate preference away from fatty acids toward glucose is observed in hypertrophic and failing hearts, and the decrease in fatty acid oxidation is not fully compensated for by an increase in glucose oxidation. Yamauchi et al demonstrated that adiponectin stimulates both glucose metabolism and utilization and fatty-acid oxidation via the AMPK signaling pathway.

The third possibility is the antifibrotic effect. Several studies have indicated that AMPK activation inhibits protein synthesis through effects on both the eEF-2 and mTOR pathways. Furthermore, metformin attenuated fibrosis and reduced the TGF-β1 mRNA level.

How Important Are Plasma Adiponectin Levels in ADHF Patients?

Heart failure itself is an insulin-resistant state, and it is reported that plasma adiponectin levels are negatively correlated with insulin resistance. Although the precise mechanisms are unknown, a decrease in plasma adiponectin levels will worsen the cardiac function in patients with heart failure and DM, and this finding indicates that treatment with carperitide may be useful for ADHF, especially in patients with DM. Further studies will be needed to examine this point.

Recently, adjunctive, acute-phase treatment with carperitide (0.025 μg·kg⁻¹·min⁻¹ for 3 days) after reperfusion therapy in patients with acute myocardial infarction (AMI) reduced the infarct size by 14.7%, increased the left ventricular ejection fraction during the chronic phase, and decreased the incidence of cardiac death and admission to hospital because of heart failure.

Kojima et al reported that plasma adiponectin levels in patients with AMI decreased significantly at 24 h and 72 h compared with the levels on admission. The plasma adiponectin levels almost returned to the levels on admission on Day 7 after the onset of AMI. The reduction of plasma adiponectin levels during the course of AMI were significantly correlated to the plasma C-reactive protein levels. These results suggest that the decrease in the plasma adiponectin levels contribute to myocardial damage, resulting in decreased left ventricular function. Therefore, administration of carperitide may decrease the infarct size via adiponectin in patients with AMI. Drugs that increase plasma adiponectin levels, such as carperitide, or activate AMPK, such as metformin, may provide a novel strategy for the treatment of ADHF, including AMI in clinical settings.

References