Adiponectin Resistance in Heart Failure and the Emerging Pattern of Metabolic Failure in Chronic Heart Failure

Jochen Springer, PhD; Stefan D. Anker, MD, PhD; Wolfram Doehner, MD, PhD

In recent years, an interesting shift in our understanding of chronic heart failure (CHF) pathophysiology may be observed. Beyond the traditional concepts of hemodynamic failure and neuroendocrine activation, it is increasingly appreciated that CHF is a much more complex and truly systemic disease including the peripheral organs and whole body regulatory processes as well. Novel concepts such as the systemic inflammatory immune activation and the skeletal muscle hypothesis have emerged. These concepts recognize the significant contribution of peripheral changes to symptomatic status, disease progression, and outcome in CHF.

A further novel facet in heart failure pathophysiology has emerged recently because impaired regulation of systemic metabolic balance is increasingly in the focus of clinical research. The emerging picture suggests a complex but characteristic pattern of metabolic pathways that are imbalanced, attenuated, or abnormally activated. Hormonal imbalances have been previously observed as common features in CHF, such as insulin resistance and growth hormone resistance that contribute to both morbidity and mortality of patients.

The metabolic interaction of neuroendocrine activation and immune activation such as from cytokines and oxygen radical accumulation add to the complexity of these interrelated processes. In general, the findings repeat, again, the classical concept of short-term beneficial adaptive responses on acute injury or disease may eventually turn into harmful maladaptive signals on prolonged and chronic activation. The overall clinical effects that may be observed from impaired energy metabolic efficacy contribute to impaired exercise capacity, muscle fatigue, and early exhaustion—key symptoms in heart failure. Furthermore, a global catabolic/anabolic imbalance has been observed leading to tissue wasting and ultimately to cachexia.

In this issue of Circulation: Heart Failure, van Berendoncks et al describe the fat tissue–derived hormone adiponectin as another addition to the emerging concept of metabolic failure in CHF. Adiponectin is a key adipokine that together with leptin and resistin contributes mainly to the regulation of energy homeostasis by improving insulin sensitivity. It also exerts multiple further actions in the human body. It increases endothelial function, and it has antiapoptotic and anti-inflammatory as well as antiatherogenic properties. Circulating adiponectin in human plasma may form oligomers and multimers or exists in monomers. Although the exact role of these isoforms is unclear, it seems that high-molecular-weight adiponectin is of particular importance as it binds to the AdipoR1 that is mainly expressed in skeletal muscle and to the AdipoR2 expressed in the liver to exert insulin-sensitizing and vasoprotective effects.

Adiponectin is mainly secreted from adipose tissue and is abundant in plasma compared with many hormones. In adults, adiponectin levels are inversely related to the amount of adipose tissue. The expression of adiponectin can be regulated by several signaling pathways. Cell culture studies have revealed a downregulation of its expression by oxidative stress, activity of the sympathetic nervous system and proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6. Moreover, lower adiponectin levels have been associated with age, gender, and smoking status, whereas exercise and a Mediterranean diet increase its expression.

Although adiponectin is thought to be expressed mainly in adipose tissue, an expression in skeletal muscle and cardiomyocytes also has been described. Yet it is unclear, how much of this nonadipose expression contributes to the circulating levels of adiponectin. In their current study, van Berendoncks et al describe a 5-fold increase in the adiponectin expression in skeletal muscle cells of patients with mild to moderate CHF. In turn, a decreased receptor expression of AdipoR1 was observed. The authors also describe a reduced expression of downstream signaling molecules like PPAR-α or AMPK and target genes in lipid and glucose metabolism. The higher than normal hormone levels together with reduced signaling efficacy suggest indeed the presence of an adiponectin resistance in skeletal muscle tissue in CHF.

These findings are of particular importance, because the role of adiponectin in heart failure is somewhat controversial. Low circulating levels of adiponectin are associated with obesity, diabetes mellitus, and coronary artery disease as well as an increased risk of myocardial infarction, whereas increased levels appear to reduce the overall cardiovascular risk. However, neither low nor high adiponectin levels were associated with the new onset of heart failure, although high levels in established heart failure have been associated with an increased severity of the disease as well as adverse outcome. Given the positive effects of adiponectin on...
insulin sensitivity, the findings of van Berendonck et al may be in line with the insulin resistance that has been observed in CHF.

In end-stage heart failure, a subgroup of patients develops the severe syndrome of cardiac cachexia that negatively affects clinical outcome and patients’ quality of life. The observed weight loss in cardiac cachexia seems to be the connective link to the altered adiponectin expression, inasmuch as the reduction of body weight may upregulate the expression of adiponectin, thus reflecting the hypercatabolic state. Indeed, significantly higher adiponectin levels compared with noncachectic heart failure patients have been reported in cardiac cachexia, which showed positive correlations with B-type natriuretic peptide and the observed weight loss. Of interest, insulin sensitivity is not better but rather worse in cachectic patients, suggesting partial uncoupling of these hormonal signals.

These findings by van Berendonck et al are in accord with the blunted metabolic regulation in CHF, such as resistances to growth hormone and insulin proposing a further desensitized metabolic signaling system. Further, a tissue-specific resistance to another adipokine—leptin has been suggested in obese individuals, where the resistance to leptin occurs only in the hypothalamus, resulting in a lack of control in feeding behavior, but no resistance is found in peripheral tissues.

As outlined earlier, adiponectin itself is regarded as an insulin sensitizer. Pharmacological insulin sensitizers such as thiazolidinediones that are widely used in the therapy of type 2 diabetes mellitus can increase the circulating levels of adiponectin in humans. On a cellular level, adiponectin improves insulin-mediated glucose uptake in skeletal muscle and reduces muscle triglyceride content by promoting its oxidation. So the decrease of AdipoR1 expression and its downstream signaling in heart failure patients described by van Berendonck et al is in accordance with the substrate change toward fatty acids seen in muscle of heart failure patients, which may result in endoplasmatic reticulum stress and ultimately in apoptosis in cardiac and skeletal muscle.

In conclusion, the study by van Berendonck et al adds to the emerging pattern of metabolic failure as characteristic feature within heart failure pathophysiology. It provides novel evidence that adiponectin resistance occurs in skeletal muscle in CHF. Whether adiponectin expression in skeletal muscle and circulating levels of adiponectin can be used as a biomarker to evaluate muscle wasting in CHF and especially cardiac cachexia remains to be proven. Moreover, given the controversial data on the role of adiponectin in heart failure, it may be to early to hypothesize whether adiponectin or its resistance may be suitable therapeutic targets in cardiovascular disease or in patient subgroups such as in cardiac cachexia. Although this current article is a big step forward, clearly further research is required to fully understand the complex molecular mechanism regulating adiponectin synthesis and signaling in CHF.

Disclosures
Dr Springer has been a consultant to Myotec Therapeutics. Dr Anker has been a consultant to Amgen Inc, Fresenius Kabi, Myotec Therapeutics, Professional Dietetics, and Vifor Pharma and received honoraria for speaking from Amgen Inc, Fresenius Kabi, and Vifor Pharma. Dr Döhner reports no conflicts.

References

Key Words: heart failure • metabolism • chronic heart failure • adipokine • resistance • hormonal imbalance
Adiponectin Resistance in Heart Failure and the Emerging Pattern of Metabolic Failure in Chronic Heart Failure
Jochen Springer, Stefan D. Anker and Wolfram Doehner

Circ Heart Fail. 2010;3:181-182
doi: 10.1161/CIRCHEARTFAILURE.110.945063
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/3/2/181

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/