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Plasma adiponectin in heart failure with and without cachexia: Catabolic signal linking catabolism, symptomatic status, and prognosis

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Abstract *Background and aims:* Adiponectin (ADPN) as an adipose tissue hormone contributes to regulation of energy metabolism and body composition and is associated with cardiovascular risk profile parameters. Cardiac cachexia may develop as a result of severe catabolic derangement in chronic heart failure (CHF). We aimed to determinate an abnormal ADPN regulation as a link between catabolic signalling, symptomatic deterioration and poor prognosis.

Abbreviations: ADPN, adiponectin; AT, anaerobic threshold; BMI, body mass index; cCHF, cachectic chronic heart failure; CHF, chronic heart failure; DEXA, dual energy X-ray absorptiometry; HOMA, homoeostasis model assessment; LVEF, left ventricular ejection fraction; ncCHF, non-cachectic chronic heart failure; NYHA, New York Heart Association; proANP, pro-atrial natriuretic peptide; peakVO_2, peak oxygen uptake; RER, respiratory exchange ratio; VE, ventilation volume per minute; VCO_2, exhaled carbon dioxide; VO_2, oxygen intake; VO_2 at AT, oxygen intake at anaerobic threshold.

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Methods and results: We measured plasma ADPN in 111 CHF patients (age 65 ± 11, 90% male, left ventricular ejection fraction (LVEF) 36 ± 11%, peak oxygen consumption (peakVO_2) 18.1 ± 5.7 l/kg*min, body mass index (BMI) 27 ± 4 kg/m^2, all mean ± standard deviation) and 36 healthy controls of similar age and BMI. Body composition was assessed by dual energy X-ray absorptiometry, insulin sensitivity was evaluated by homoeostasis model assessment, exercise capacity by spiroergometry. Plasma ADPN did not differ between CHF vs. controls (13.5 ± 11.0 vs. 10.5 ± 5.3 mg/l, $p > 0.4$), but increased stepwise with NYHA functional class (I/II/III: 5.7 ± 1.4/10.7 ± 8.3/19.2 ± 14.0 mg/l, ANOVA $p < 0.01$). Furthermore, ADPN correlated with VO_2 at anaerobic threshold ($r = -0.34$, $p < 0.05$). ADPN was highest in cachectic patients (cCHF, 16%) vs. non-cachectic (ncCHF) (18.7 ± 15.0 vs. 12.5 ± 9.9 mg/l; $p < 0.05$). ADPN indicated mortality risk independently of established prognosticators (HR: 1.04 95% CI: 1.02−1.07; $p < 0.0001$). ADPN above the mean (13.5 mg/l) was associated with a 3.4 times higher mortality risk in CHF vs. patients with ADPN levels below the mean.
Conclusion: Circulating ADPN is abnormally regulated in CHF. ADPN may be involved in impaired metabolic signalling linking disease progression, tissue wasting, and poor outcome in CHF.

Background

Chronic heart failure (CHF) is a constantly growing problem due to an increasing incidence, prevalence and economic burden [1]. Regardless of improvements in treatment, CHF persists to carry a highly impaired prognosis [2]. Over the last two decades, the pathophysiological concept of CHF has evolved from a single-organ defect to a systemic disorder involving neuroendocrine, inflammatory, immunological, and metabolic factors [3]. Impaired metabolism can lead to cardiac cachexia, a complication of advanced CHF, which is associated with severe symptomatic status and particularly grave prognosis.

In this context, adipose tissue is no longer perceived as a plain energy deposit, but rather as a physiologically active player in CHF pathophysiology [4]. It communicates with other tissues and organs via adipokines. Adipokines are small proteins, almost exclusively synthesised and secreted by adipose tissue [5]. The adipokine adiponectin (ADPN) is a 244 amino acid peptide, synthesised and secreted in large quantities by adipose tissue [6]. Its level is gender-depended and is higher in women than in men [7]. Notably, *high* ADPN concentrations are associated with *low* body fat [7]. A key role of ADPN is to modify energy metabolism. In the liver, ADPN increases insulin sensitivity and reduces gluconeogenesis whereas in skeletal muscle it stimulates β-oxidation [8]. Beyond metabolic control, ADPN has been linked to classical factors defining cardiovascular risk profile. Indeed, low ADPN levels are predictive of insulin resistance, arteriosclerosis, and inflammation resulting in increased risk for coronary artery disease [9]. In healthy subjects, high ADPN levels are associated with a protective cardiovascular effect, low blood pressure, lower total and LDL-cholesterol, low body mass index (BMI) as well as with high insulin sensitivity and high HDL-cholesterol [7,10].

Recently, several studies on the role of ADPN in CHF have been focused on mortality [11,12], functional capacity [13], or metabolism [14]. Impaired metabolic balance, reduced symptomatic status, and poor prognosis culminate in cardiac cachexia. We hypothesised abnormal ADPN regulation to be an accountable signal in CHF linking catabolic regulation with clinical disease progression. The aim of the present study was to assess, in a combined approach, ADPN as a link between impaired metabolism, advanced symptomatic status in CHF and poor prognosis.

Methods

Patients

In this study 111 non-diabetic patients with systolic CHF of ischaemic or non-ischaemic aetiology were included. All patients presented with an impaired LVEF ≤45%, with a disease history of at least 6 months and NYHA class I−III. Cachexia was diagnosed as defined previously: BMI below 20 kg/m^2 or a weight loss of ≥5% within one year, plus the presence of abnormal biochemical parameters [15]. Patients were in stable ambulatory condition and on standard medical therapy for HF. Thirty-six healthy volunteers of similar BMI and age served as a control group. The research protocol was approved by the local ethics committee and written informed consent was obtained from all subjects.

Spiroergometric exercise testing

A symptom-limited spiroergometric exercise test was performed on a treadmill according to the modified Bruce protocol [16]. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and ventilation per minute (VE) were measured breath-by-breath (MedGraphics, MN, USA). Subjects were encouraged to exercise until exhaustion and exercise time, peak oxygen uptake (peakVO_2 ml/min/kg) and ventilatory efficiency (VE/VCO_2-slope) were assessed. Respiratory exchange ratio (RER), a marker of exhaustion, was calculated from peakVCO_2 and peakVO_2. The anaerobic threshold (AT) was assessed by evaluating VE/VCO_2-slope, VE/VO_2-slope, and RER.