

## Original Article

# The influence of increasing serum adipose tissue hormone on chronic heart failure combined with sleep apnea syndrome

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**Abstract:** Objective: The aim was to investigate serum levels of adiponectin (APN) and complement C1q tumor necrosis factor related protein 1 (CTRP1) and to explore their connection to disease in chronic heart failure (CHF) patients with or without sleep apnea syndrome (SAS). Methods: We assayed serum levels of APN, CTRP1, high-sensitivity C-reactive protein (hs-CRP), and N-terminal pro-brain natriuretic peptide (NT-proBNP). We also evaluated the left ventricular volumes and function in 62 SAS and 62 non-SAS patients with CHF, while 62 healthy subjects were enrolled into a control group. Result: As a result, serum APN and NT-proBNP levels were higher ( $P < 0.05$ ) in CHF patients than in healthy subjects, with higher levels of APN, CTRP1, hs-CRP, and NT-proBNP in patients with SAS than those without ( $P < 0.05$ ). For all CHF patients, serum APN levels correlated positively with NT-proBNP values, left ventricular volumes, and the identified New York Heart Association (NYHA) functional class. For CHF patients with SAS, serum levels of CTRP1 correlated positively with hs-CRP and low-density lipoprotein cholesterol (LDL-c). APN was determined to be an independent risk factor for patients with CHF ( $P < 0.05$ ), while CTRP1 was an independent influencing factor for serum APN levels ( $P < 0.05$ ). Conclusion: Increased serum APN levels are related to the severity of CHF, while SAS appears to intensify the disease process and increase serum CTRP1 level. Such associations may be clinically important and are worthy of further investigation.

**Keywords:** Chronic heart failure, sleep apnea syndrome, adiponectin, complement C1q tumor necrosis factor related protein 1

## Introduction

Chronic heart failure (CHF) is a pathophysiological process that is influenced by neuro hormones and cardiac remodeling, which occurs in vicious circle, increasing morbidity and mortality gradually [1]. Adiponectin (APN) is a hormone that is derived from adipose tissue and is sensitive to insulin, while helping to regulate energy metabolism by improving the oxidation of free fatty acids in skeletal muscle and enhancing gluconeogenesis in the liver [2]. Ultimately, adiponectin exerts anti-inflammatory and anti-oxidative effects help to protect the cardiovascular system [3].

This insulin-sensitizing hormone, adiponectin, belongs to the ever expanding C1q/tumor

necrosis factor (TNF) family of proteins [4]. Like adiponectin, all secreted complement C1q tumor necrosis factor related proteins (CTRP) form trimers as their basic structural units [5]. Functional characterization of one such family member, CTRP1, showed that it specifically activates the Akt/MAPK (mitogen-activated protein kinase) signaling pathway and may be considered a novel adipokine [6]. CTRP1 is expressed predominantly by adipose tissue and is widely involved in regulating human metabolism and inflammatory immune processes [7]. CTRP1 is closely linked to cardiovascular disease; Joen et al. [8] observed that the serum levels of CTRP1 are often increased in patients with hypertension and are stimulated by aldosterone production. However, the differences in serum adiponectin and CTRP1 levels

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between CHF patients with SAS compared those without has not been previously explored, and the mechanisms by which they may function to accentuate CHF was not clear.

### Materials and methods

#### *Study population*

We restricted our inclusion criteria to Chinese patients of Han nationality with systolic chronic heart failure (HF) due to ischemic or idiopathic dilated cardiomyopathy. The study included 87 consecutive patients with ischemic HF (mean age: 68.3±9.9 years, duration of disease: 1.5±2.1 years) and 37 patients with HF caused by idiopathic dilated cardiomyopathy (mean age: 57.0±13.5 years, duration of disease: 2.9±3.3 years) that were recruited between September 2012 and May 2014 from Rui Jin Hospital, Affiliated to Shanghai Jiao Tong University School of Medicine in China. Systolic HF was diagnosed according to the European Society of Cardiology guidelines, including patients with symptoms or signs of HF and left ventricular ejection fraction (LVEF); 45% were assessed by echocardiography. For patients with idiopathic dilated cardiomyopathy and/or cardiovascular risk factors (e.g. type 2 diabetes), the presence of significant coronary artery disease was excluded by coronary angiography. Of the 124 patients with HF, 62 had SAS and others did not. Sleep apnea syndrome was assessed by polysomnography. Diabetes was defined according to the American Diabetes Association criteria as the following: two fasting plasma glucose levels ≥7.0 mmol/L, or symptoms of diabetes plus a casual post-prandial plasma glucose reading ≥11.1 mmol/L, or a 2h glucose reading ≥11.1 mmol/L after a 75 g glucose load, or taking oral hypoglycaemic drugs and/or parenteral insulin. To avoid confounding variables, we excluded patients with a history of viral myocarditis, atrial fibrillation, hypertrophic cardiomyopathy, primary valvular disease or pulmonary heart disease. We also excluded patients with type 1 diabetes, chronic viral or bacterial infections, tumors, or immune disorders. Detailed information was obtained on general demographics, clinical manifestation, and medications, as well as the New York Heart Association (NYHA) functional class, and echocardiographic measurements were used to evaluate HF severity. The gender distribution was the same as in the general population; age

was purposely matched between controls and the HF population. Detailed medical and family histories were taken, and fasting blood samples were collected during an annual physical check-up. In the control subjects, serum levels of glucose, lipid profiles, liver and renal function tests, and the electrocardiogram results were normal for all, and no patients had a history of cardiovascular diseases (including past history of angina/myocardial infarction). The study protocol was approved by the local hospital Ethics Committee, and written informed consent was obtained from all participants.

#### *Biochemical investigations*

Peripheral venous blood samples were collected after an overnight fast. Serum glucose, blood urea nitrogen, creatinine, uric acid, total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TG) were measured using standard laboratory techniques on a Hitachi 912 Analyser (Roche Diagnostics, Mannheim, Germany). Serum NT-proBNP and hs-CRP were determined using a commercially available electrochemiluminescence immunoassay kit (Roche Diagnostics). Serum APN levels were assessed with an enzyme-linked immunosorbent assay (ELISA) kit (Adiponectin ELISA kit; Demeditec Corporation, Germany) according to the manufacturer's instructions. The detection limit for APN was 0.01 µg/mL, with an inter-assay coefficient of variation <10% and an intra-assay coefficient of variation <5%. Serum CTRP1 levels were assessed with an ELISA kit (human CTRP1 ELISA kit; BioVendor Corporation, Czech Republic) according to the manufacturer's instructions. The detection limit for CTRP1 was 0.016 ng/mL, with an inter-assay coefficient of variation <10% and an intra-assay coefficient of variation <4%.

#### *Echocardiographic assessment*

Transthoracic two-dimensional echocardiography was performed using a Hewlett-Packard Sonos 2500 (Hewlett-Packard, San Diego, CA, USA) or a GE Vivid-7 system (General Electric Vingmed Sound AS, Horton, Norway) equipped with 2.5 or 1.7/3.4 MHz transducers, respectively. Images were obtained at rest with the patient lying in the left lateral decubitus position at end-expiration. Left ventricular end-dia-

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stolic and end-systolic volumes were measured according to the biplane Simpson's method, based on the American Society of Echocardiography recommendations, and LVEF was calculated. An average of three consecutive cardiac cycles was assigned for each patient.

### *Polysomnography assessment*

Polysomnography recorded subjects' apnea episodes and hypopnea index during 7 hours of sleep by Somté PSG (Somte PSG system, Compumedics, AUS). At night, sleep apnea episodes occurring 30 times or more and/or a sleep apnea hypopnea index (AHI) greater than 5 times per hour with accompanying symptoms of sleepiness were diagnosed as sleep apnea syndrome. Apnea refers to episodes when or onasal breathing airflow completely stops for more than 10 seconds during sleep, while hypopnea refers to a 50% or greater decrease in respiratory airflow intensity (amplitude) accompanied by at least a 4% decrease in oxygen saturation compared to basal levels. The sleep apnea hypopnea index refers to the average number of times apnea and hypopnea occur during sleep.

### *Follow-up*

All HF patients were prescribed standard HF treatments and were seen every 1-3 months at a dedicated HF clinic. During each visit, the patient's heart rate, blood pressure, and new clinical manifestations were recorded, while echocardiography was performed every 6 months. Adverse events (hospitalization or death from HF) were recorded during each visit or were reported/confirmed by telephone with patients or their family members. Hospitalization for HF was typically the result of progressive fluid retention and/or the need to increase or change medications. Two trained physicians independently reviewed all the medical notes, including forms from visits to the emergency department and hospital medical records.

### *Statistical analysis*

Continuous variables are presented as mean  $\pm$  standard deviation (SD). Differences between groups were compared with two-factor (CHF, SAS) analysis of variance followed by a Dunnett post hoc between-group analysis or by the non-parametric Kruskal-Wallis test. Categorical

data were summarized as frequencies or percentages, and the differences between groups were evaluated by the Chi-square test. The sample size (124 patients with CHF and 62 subjects without CHF) was such to yield 80% power to detect differences between CHF and non-CHF patients or SAS and non-SAS patients for APN, NT-proBNP, CTRP1, and hs-CRP (for all, 99% power, both in non-SAS and SAS patients) under a type I error probability of 0.05 (12a) for a two-sided test.

Correlations of serum APN and CTRP1 (on a logarithmic scale) with other biomarkers or echocardiographic measurements were assessed by Pearson's test, and associations of these biomarkers with NT-proBNP and hs-CRP (not normally distributed) or NYHA functional class (categorical variable) were determined by Spearman's test. The linear correlation between NT-proBNP and hs-CRP with APN and CTRP1 was represented with Pearson's method to show the crude distribution. We used two models in multivariable logistic regression analysis to evaluate the presence of CHF in non-SAS and SAS patients. In Model I, multivariable adjustment was made for conventional risk factors measured at baseline examination, which included age, gender, smoking, hypertension, systolic/diastolic blood pressure, triglycerides, total cholesterol, blood urea nitrogen, creatinine, uric acid, fasting glucose, and glycated haemoglobin (by a conditional logistic regression method). In Model II, the multivariable-adjusted odd ratios (ORs) and their 95% confidence intervals (CI) for CHF associated with the biomarkers of interest were compared with the respective normal- and SAS-matched controls and synchronously estimated together with significantly independent conventional risk factors established in Model I (by the backward conditional logistic regression method). In addition, the ORs were given for a 1- or 1/2-SD increase of each biomarker, blood pressure, creatinine, and uric acid level in the control group. All statistical analyses were performed using SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA).

## **Results**

### *Clinical characteristics*

Patients with CHF were frequently male smokers with diabetes, the prevalence of which was

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**Table 1.** Baseline clinical characteristics and biochemical assessments of patients studied

	Non SAS N=62	SAS N=62	P	CHF N=124	Control N=62	P
Male/female (n)	52/10	51/11	0.944	103/21	52/10	0.965
Age (years)	61.9±10.1	63.6±11.5	0.353	62.7±10.8	63.6±10.7	0.722
Aetiology (ischaemic/dilated cardiomyopathy, n)	43/19	44/18	0.921	87/37		
Hypertension [n (%)]	42 (67.7)	42 (67.7)	0.95	84 (67.7)	41 (66.1)	0.764
Diabetes [n (%)]	19 (31.4)	24 (41.2)	0.234	43 (34.7)	0 (0)	<0.001
Dyslipidemia [n (%)]	27 (42.9)	23 (36.8)	0.465	50 (40.3)	0 (0)	<0.001
Smoking [n (%)]	20 (32.2)	18 (29.1)	0.832	38 (30.6)	4 (0.1)	0.022
NYHA function class I/II/III/IV (n)	0/34/26/2	0/32/28/2	0.885	0/66/54/4	16/0/0/0	<0.001
Systolic blood pressure (mmHg)	125.6±16.8	126.6±15.2	0.698	126.1±16	125.7±10.6	0.867
Diastolic blood pressure (mmHg)	77.2±12.0	78.3±11.4	0.565	77.7±11.7	79.3±7.8	0.376
Heart rate (b.p.m.)	74.5±14.9	72.8±12.7	0.481	73.7±13.8	77.1±8.0	0.077
Body mass index (kg/m <sup>2</sup> )	23.9±3.4	24.3±3.4	0.508	24.1±3.4	23.4±2.8	0.304
hs-CRP (mg/L)	4.75±3.63	9.37±7.51	0.026	6.57± 4.29	5.72±3.93	0.181
NT-proBNP (pg/ml)	3229.1±1367.2	5207.5±2191.8	0.152	4309.3±2019.8	329.1±217.2	<0.05
Left atrial diameter (mm)	39.9±3.5	45.9±3.8	0.043	42.4±3.7	41.6±4.1	0.362
Left ventricular end-systolic volume (mL)	296±115.6	303.3±120.1	0.586	299.3±119.3	105.3±23.7	<0.05
Left ventricular end-diastolic volume (mL)	153.7±64.8	155.2±61.3	0.719	154.2±62.7	36.3±11.9	<0.05
Ejection fraction (%)	36.6±7.4	38.5±7.1	0.126	37.5±7.3	65.0±4.4	<0.001
Fasting glucose (mmol/L)	5.8±1.83	5.81±1.87	0.991	5.81±1.85	5.33±1.14	0.203
Glycated haemoglobin (%)	6.6±1.3	6.6±1.4	0.928	6.6±1.4	6.3±1.2	0.263
Blood urea nitrogen (mmol/L)	6.3±2.4	6.7±5.5	0.592	4.9±0.7	4.9±1.0	0.533
Creatinine (mmol/L)	90.7±46.2	90.5±25.6	0.966	78.2±12.7	76.6±10.9	0.534
Uric acid (mmol/L)	397.8±119.3	389.6±124.7	0.695	352.6±56.8	347.6±45.6	0.663
Triglycerides (mmol/L)	1.92±1.16	1.56±1.1	0.064	1.75±1.14	1.59±0.66	0.541
Total cholesterol (mmol/L)	4.35±1.03	4.33±0.88	0.889	4.34±0.96	4.29±0.49	0.672
High-density lipoprotein cholesterol (mmol/L)	1.12±0.3	1.18±0.3	0.173	1.15±0.3	1.18±0.25	0.581
Low-density lipoprotein cholesterol (mmol/L)	2.48±0.84	2.5±0.76	0.885	2.9±0.72	2.87±0.75	0.856
Angiotensin-converting enzyme-inhibitors [n (%)]	47 (75.8)	45 (72.6)	0.403	92 (74.2)	22 (35.4)	0.024
Angiotensin receptor blockers [n (%)]	11 (17.7)	12 (19.4)	0.768	23 (18.5)	8 (12.9)	0.166
β-Blockers [n (%)]	60 (96.8)	59 (95.2)	0.953	119 (96)	25 (40.3)	<0.001
Nitrates [n(%)]	42 (67.7)	41 (66.1)	0.811	83 (66.9)	3 (5)	<0.001
Diuretics [n (%)]	36 (58.1)	38 (61.3)	0.43	74 (59.7)	8 (12.9)	<0.001
Digoxin [n (%)]	48 (77.4)	46 (74.2)	0.63	94 (75.8)	3 (5)	<0.001
Statins [n (%)]	12 (19.4)	16 (25.8)	0.271	28 (21.9)	10 (16.1)	0.146
Aspirin [n (%)]	47 (75.8)	50 (80.6)	0.156	97 (78.2)	15 (24.2)	0.038
Hospitalization during the 1-year follow-up [n (%)]	6 (9.7)	12 (19.4)	0.045	18 (14.5)	0 (0)	
Death during the 1-year follow-up [n (%)]	0 (0)	3 (4.8)	0.038	3 (2.4)	0 (0)	

Values are given as mean ± standard deviation or number (percentage). SAS, sleep apnea syndrome; CHF, chronic heart failure; hs-CRP, high-sensitivity C-reactiveprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

higher than in the control group. No significant differences between CHF patients with and without SAS were observed for left ventricular end-diastolic and end-systolic volumes or LVEF, with the exception of a larger left atrial size in SAS patients with CHF (**Table 1**).

### *Influence of heart failure and its etiology on biological analyses*

Serum levels of APN (5.89±3.36 vs. 3.78±1.28 µg/mL) and NT-proBNP (4309.3±2019.8 vs. 329.1±217.2 pg/mL) were higher in patients

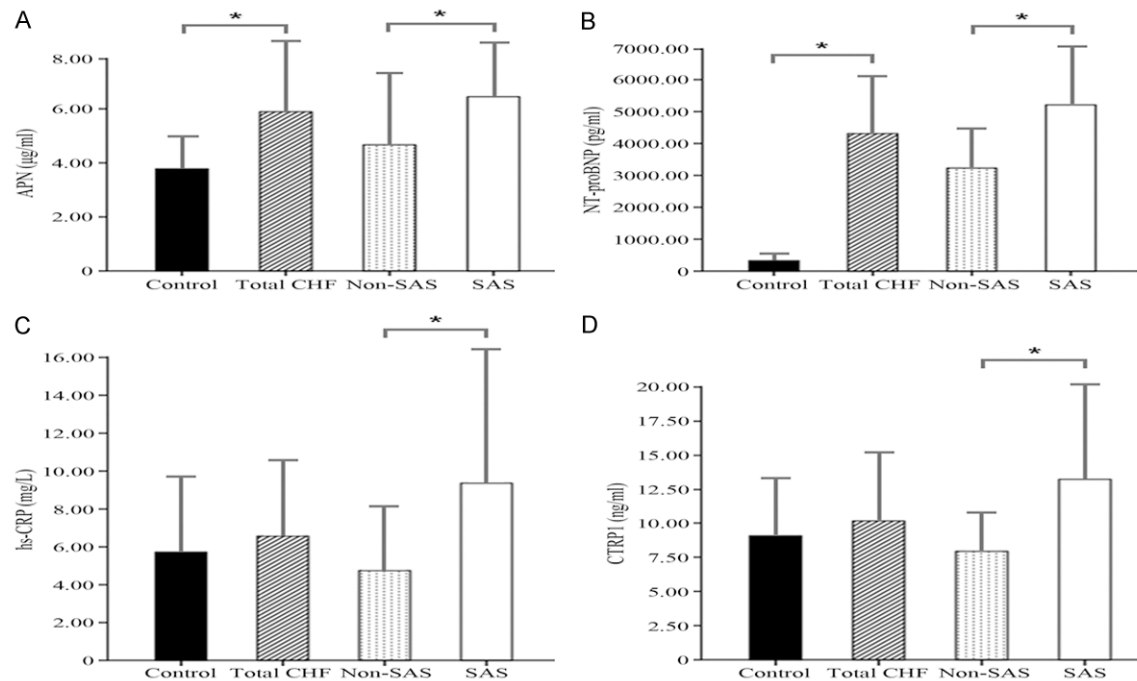
with CHF than in those without CHF (P<0.05), while levels of hs-CRP (9.37±7.51 vs. 4.75±3.63 mg/L), APN (6.45±2.61 vs. 4.67±2.58 µg/mL), NT-proBNP (5207.5±2191.8 vs. 3229.1±1367.2 pg/mL), and CTRP1 levels (13.20±7.61 vs. 7.93±3.32 ng/mL) were elevated in CHF patients with SAS compared to CHF patients without SAS (P<0.05). Ultimately, levels of APN and NT-proBNP, in contrast to the other factors analyzed, were selectively influenced by the presence of CHF and SAS (**Table 2; Figure 1**).

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**Table 2.** Serum levels of biological analysis in SAS and non-SAS patients with or without CHF

	Non SAS N=62	SAS N=62	P	CHF N=124	Control N=62	P
Adiponectin (ug/ml)	4.67±2.58	6.45±2.61	0.034	5.89±3.36	3.78±1.28	0.028
CTRP1 (ng/ml)	7.93±3.32	13.20±7.61	0.017	10.15±5.01	9.06±4.73	0.32
hs-CRP (mg/L)	4.75±3.63	9.37± 7.51	0.01	6.57± 4.29	5.72±3.93	0.511
NT-proBNP (pg/ml)	3229.1±1367.2	5207.5±2191.8	0.013	4309.3±2019.8	329.1±217.2	<0.001

Values are given as mean ± standard deviation. SAS, sleep apnea syndrome; CHF, chronic heart failure; CTRP1, C1q tumor necrosis factor related protein 1; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide.



**Figure 1.** Comparison of serum levels of APN, CTRP1, hs-CRP and NT-proBNP among SAS and non-SAS patients with or without CHF. APN, adiponectin; CTRP1, C1q tumor necrosis factor related protein 1; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; SAS, sleep apnea syndrome; CHF, chronic heart failure.

**Table 3.** Serum levels of biological analysis according to different heart failure aetiology

	Ischaemic cardiomyopathy (ICM)	Dilated cardiomyopathy (DCM)	P
Adiponectin (ug/ml)	6.01±3.41	5.77±3.3	0.66
CTRP1 (ng/ml)	12.27±6.79	8.37±3.72	0.031
hs-CRP (mg/L)	9.51±5.93	5.03±3.10	0.02
NT-proBNP (pg/ml)	4410.1±1999.5	4279.8±2033.0	0.742

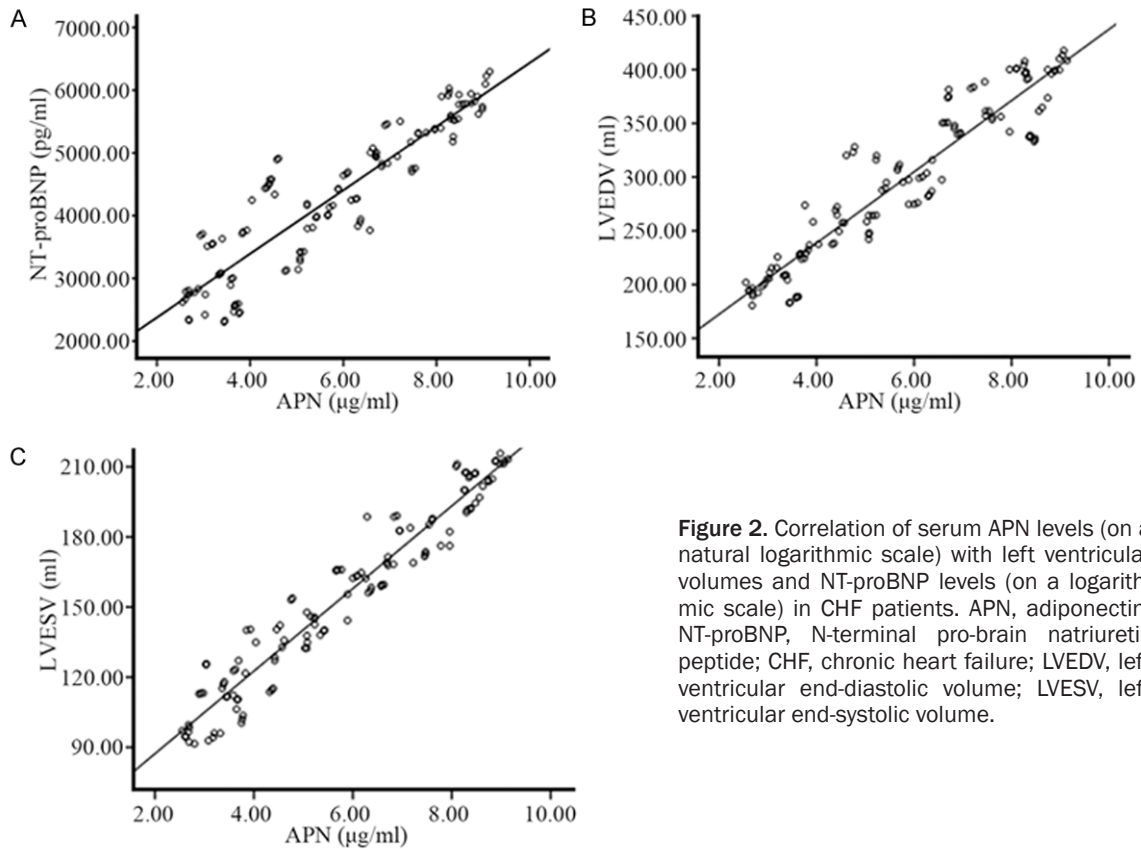
Values are given as mean ± standard deviation. CTRP1, C1q tumor necrosis factor related protein 1; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Higher levels of hs-CRP and CTRP1 were observed in CHF patients with SAS compared to those without SAS ( $P < 0.01$ ). In addition, hs-

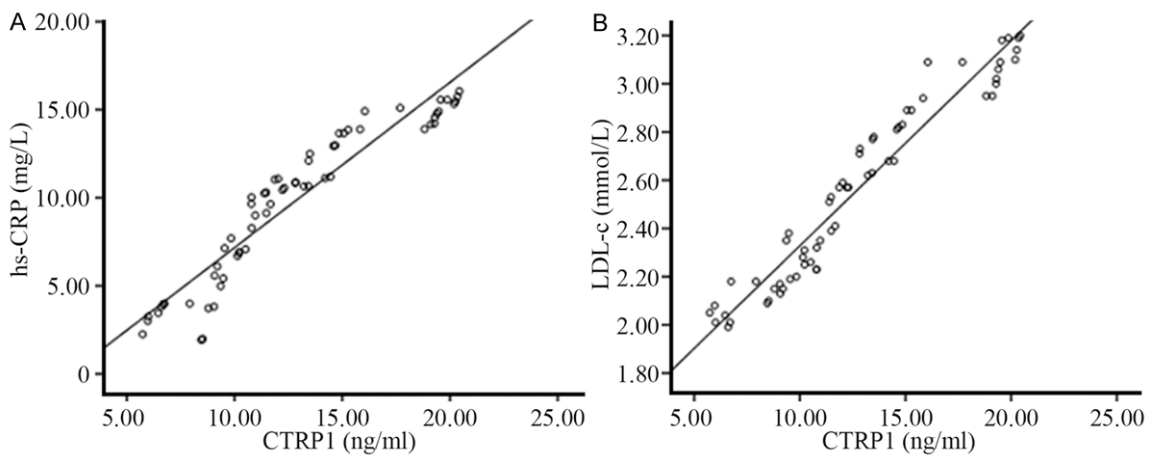
CRP ( $9.51 \pm 5.93$  vs.  $5.03 \pm 3.10$  mg/L) and CTRP1 ( $12.27 \pm 6.79$  vs.  $8.37 \pm 3.72$  ng/mL) levels were related to the etiology of CHF, with higher levels occurring in ischemic vs. dilated cardiomyopathy patients ( $P < 0.05$ ). However, APN and NT-proBNP levels were not influenced by etiology (Table 3).

Serum APN levels were positively correlated with NT-proBNP (Pearson's  $r = 0.208$ ;  $P < 0.05$ ), left ventricular end-diastolic and end-systolic volumes in CHF patients ( $r = 0.267$  and  $r = 0.321$ , respectively;  $P < 0.001$ ) (Figure 2). In CHF patients, APN lev-

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**Figure 2.** Correlation of serum APN levels (on a natural logarithmic scale) with left ventricular volumes and NT-proBNP levels (on a logarithmic scale) in CHF patients. APN, adiponectin; NT-proBNP, N-terminal pro-brain natriuretic peptide; CHF, chronic heart failure; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.



**Figure 3.** Correlation of serum CTRP1 levels (on a natural logarithmic scale) with hs-CRP and LDL-c (on a logarithmic scale) in CHF patients. CTRP1, C1q tumor necrosis factor related protein 1; hs-CRP, high-sensitivity C-reactive protein; LDL-c, low-density lipoprotein cholesterol; CHF, chronic heart failure.

els were also positively correlated with NYHA functional class (Pearson's  $r=0.186$ ;  $P<0.05$ ), while serum CTRP1 levels showed a positive correlation with hs-CRP (Pearson's  $r=0.214$ ;  $P<0.05$ ) and LDL-c (Pearson's  $r=0.277$ ;  $P<0.05$ ) in CHF patients with SAS (Figure 3; Table 4).

### *Multivariable logistic regression analysis for the presence of heart failure*

Multivariable stepwise logistic regression analysis was performed for all subjects, with or without CHF. Analysis revealed that, adjusting

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**Table 4.** Association of biological analysis with disease severity in heart failure patients

Variables correlated	Total CHF patients		Non-SAS patients with CHF		SAS patients with CHF	
	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
APN-NT-proBNP	0.727	<0.001	0.749	<0.001	0.713	<0.001
APN-LVEDV	0.733	<0.001	0.750	<0.001	0.708	<0.001
APN-LVESV	0.652	<0.001	0.694	<0.001	0.623	<0.001
APN-LVEF	-0.056	0.082	-0.063	0.101	-0.049	0.09
APN-NYHA class	0.288	0.014	0.291	0.02	0.275	0.018
CTRP1-NT-proBNP	0.022	0.211	0.025	0.134	0.020	0.188
CTRP1-LVEDV	0.076	0.096	0.082	0.183	0.075	0.207
CTRP1-LVESV	0.037	0.142	0.033	0.151	0.041	0.253
CTRP1-LVEF	-0.081	0.096	-0.079	0.173	-0.092	0.324
CTRP1-NYHA class	0.125	0.23	0.116	0.109	0.175	0.468

SAS, sleep apnea syndrome; CHF, chronic heart failure; APN, adiponectin; CTRP1, C1q tumor necrosis factor related protein 1; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

for traditional cardiovascular risk factors (Model I), smoking, blood urea nitrogen, and systolic blood pressure were all independent determinants of CHF, while hs-CRP, systolic blood pressure, and LDL-c were independent risk factors for CHF in SAS patients. When NT-proBNP, APN, and CTRP1 measurements were considered with the above risk factors in the multivariable analysis (Model II), APN and NT-proBNP were independently associated with the presence of CHF in all subjects, while CTRP1 was specifically associated with the presence of CHF in SAS patients (Table 5).

### *Regression analysis of the relationship between serum adiponectin and clinical grades, biochemical, and biological markers*

When possible influential factors were set in the linear regression equation as independent variables ( $P < 0.05$ ), while adiponectin was considered the dependent variable. Age, gender, systolic blood pressure, HbA1c, uric acid, TC, LDL-c, LVEF, and hypertension were found not to be correlated with adiponectin levels. However, the cardiac function grade, NT-proBNP, and CTRP1 levels were positively correlated with adiponectin ( $P < 0.05$ , Table 6).

### *Association of biological analysis with mortality*

During a year of follow-up, 4 patients did not complete the study, such that the dropout rate was 2.44%. Twenty-one patients had MCE (the refractory heart failure readmission rate was

61.9%). The incidence of MCE was also higher in CHF patients with SAS ( $P = 0.041$ ). After correcting the following risk factors: gender, age, hypertension, coronary heart disease, diabetes, atrial fibrillation, anemia, chronic renal insufficiency, cardiac function grade, and NT-proBNP, COX regression analysis showed that adiponectin was still an independent predictor of death in CHF patients ( $P < 0.05$ ,  $RR = 1.247$ , 95% CI: 1.026-1.517).

### **Discussion**

The CTRP family belongs to a protein secretion family, mainly derived from adipose stromal cells [7]. The members of the CTRP family exert various and complex functions in response to inflammation or the resolution of inflammation. CTRP1 is secreted by various tissues, which ultimately intensifies inflammation [9]. Kim et al. [10] found that CTRP1 expression levels increase in adipose tissues when rats are injected with bacterial lipopolysaccharides, which is related to the combined effects of TNF- $\alpha$  and IL-1 $\beta$  release. Abnormally elevated levels of angiotensin II prompted adrenal glomerulosa cells to release CTRP1, which stimulated the synthesis of aldosterone [7].

This research indicates that serum level of CTRP1 in CHF patients with SAS were higher than in patients without SAS, while CTRP1 levels were positively correlated with the severity of disease. Recent research indicates that CTRP1 levels are associated with chronic inflammation and are involved in stimulating

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**Table 5.** Multivariable stepwise logistic regression model for the presence of heart failure

Variables	Total CHF patients		SAS patients with CHF	
	OR (95% confidence interval)	P-value	OR (95% confidence interval)	P-value
Univariable conditional logistic regression adjusting for conventional risk factors (Model I)				
Male/female	1.139 (1.054-1.606)	0.341	1.012 (0.870-1.877)	0.493
Age (years)	0.962 (0.874-1.295)	0.474	1.289 (0.860-1.931)	0.219
Smoking	2.235 (1.455-4.582)	0.009	1.211 (0.882-1.732)	0.054
Systolic blood pressure	1.386 (1.194-1.771)	0.007	1.229 (1.149-1.505)	0.011
Diastolic blood pressure	1.422 (1.255-1.793)	0.177	2.017 (1.889-3.126)	0.553
Body mass index	2.877 (0.999-6.351)	0.15	1.621 (0.636-4.134)	0.312
hs-CRP	1.350 (1.231-1.927)	0.629	1.414 (1.268-1.613)	0.012
Fasting glucose	1.274 (1.145-3.094)	0.746	1.342 (0.889-1.656)	0.44
Glycatedhaemoglobin	2.311 (1.657-4.883)	0.423	1.652 (1.115-3.627)	0.237
Blood urea nitrogen	1.596 (1.162-2.193)	0.004	1.155 (1.067-1.837)	0.461
Creatinine	2.016 (1.826-5.021)	0.783	1.732 (0.992-2.553)	0.351
Uric acid	1.906 (1.767-2.865)	0.193	1.569 (1.387-1.765)	0.452
Triglycerides	1.367 (1.101-1.552)	0.076	1.630 (0.920-2.412)	0.661
Total cholesterol	2.131 (1.671-2.263)	0.187	1.031 (0.838-1.156)	0.091
High-density lipoprotein cholesterol	0.632 (0.266-0.919)	0.085	0.537 (0.368-0.822)	0.172
Low-density lipoprotein cholesterol	1.476 (1.129-1.776)	0.087	2.364 (1.228-4.213)	0.008
Backward stepwise regression adjusting for independent conventional risk factors and all biomarkers (Model II)				
Smoking	1.382 (1.176-2.691)	0.36	--	--
Systolic blood pressure	1.926 (1.763-3.541)	0.679	1.738 (1.265-1.997)	0.568
hs-CRP	--	--	2.171 (1.976-3.686)	0.635
Blood urea nitrogen	1.637 (1.455-2.016)	0.577	--	--
Low-density lipoprotein cholesterol	--	--	2.382 (1.809-3.576)	0.368
NT-proBNP	1.786 (1.233-2.589)	0.025	1.555 (1.424-1.669)	0.068
APN	1.359 (1.107-1.792)	0.013	1.233 (1.105-1.764)	0.052
CTRP1	1.565 (1.237-1.981)	0.103	1.236 (1.095-1.663)	0.022

SAS, sleep apnea syndrome; CHF, chronic heart failure; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; APN, adiponectin; CTRP1, C1q tumor necrosis factor related protein 1.



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**Table 6.** Multiple regression analysis the influence factors of adiponectin

Factors	Linear regression coefficient	P	Partial regression coefficient	P
NYHA class	0.329	<0.001	0.016	0.019
Triglycerides	0.076	0.001	0.059	0.434
Total cholesterol	0.050	0.036	0.054	0.478
Fasting glucose	-0.191	0.008	0.139	0.064
Dyslipidemia	-0.305	<0.001	0.073	0.431
Diabetes	-0.168	0.044	0.119	0.146
NT-proBNP	0.438	<0.001	0.142	0.020
CTRP1	0.333	<0.001	0.053	0.008

NT-proBNP, N-terminal pro-brain natriuretic peptide; CTRP1, C1q tumor necrosis factor related protein 1.

the AMP-activated protein kinase (AMPK), serine/threonine kinase (AKT), and mitogen activated protein kinase (MAPK) signaling pathways [6]. It has also been suggested that CTRP1 may amplify local inflammation in these tissues as pro-inflammatory mediators are produced; the specific functions and molecular regulation mechanisms require further investigation.

Adiponectin belongs to the larger C1q protein family, which is defined by the presence of a C-terminal globular domain with sequence homology to the immunocomplement protein C1q [6]. The genome encodes C1q domain-containing proteins, including C1q/TNF-related proteins (CTRPs) [11]. Ultimately, we found that there are both unique and shared characteristics between CTRPs and adiponectin.

Our research demonstrates that serum adiponectin levels significantly increase in CHF patients. Currently, very few reports about have linked adiponectin to heart failure, especially in CHF with SAS. Our study confirms that serum adiponectin levels can reflect the severity of disease, in this case, heart failure. Adiponectin levels were determined to be an independent predictor of death in CHF patients. These measurements can also be used to predict the cardiac function grade, NT-proBNP, and CTRP1 levels as independent factors that influence the adiponectin concentration.

Adiponectin, a cytokine, is mainly secreted by adipose tissue and exerts apparent anti-atherosclerosis and anti-inflammatory effects. However, our study showed that serum adiponectin level increased and were an indepen-

dent predictor of death in heart failure. The possible mechanisms were as follows: 1) Adiponectin production is a sign of cardiac cachexia. Recent studies show that adiponectin has a direct effect on brain energy metabolism and may cause weight loss that can be improved with plasma adiponectin levels [12]. Hence, researchers have speculated that high plasma adiponectin is accompanied by high energy consumption and heart tissue damage in CHF patients. High adiponectin levels in CHF patients, as a marker

of this consumption process, may help to explain the relationship between high adiponectin levels and a high mortality risk in CHF patients. 2) Another mechanism indicated by our study shows that pericardial adipose tissue plays a role in the expression of adiponectin. As heart failure progresses, the heart can secrete adiponectin, which can be released into the peripheral circulation, such that the concentration of circulating adiponectin increases in patients with heart failure [13]. 3) A final mechanism involves adiponectin mRNA expression, which increases by 5-fold in the skeletal muscles of patients with CHF, while adiponectin receptor 1 is down-regulated in skeletal muscle and the activity of the downstream peroxisome proliferator activated receptor/adenosine monophosphate activated protein kinase (PPAR/AMPK) pathway is decreased [14, 15]. These findings suggest that functional adiponectin resistance was occurring, leading to increased adiponectin levels, to compensate for circulating adiponectin levels.

Our study also showed that serum adiponectin levels increased in patients with SAS; CTRP1 may promote the secretion of adiponectin by stimulating inflammation. We also observed that the adiponectin levels were positively correlated with the concentration of NT-proBNP. Based on these mechanisms, we hypothesize that the natriuretic peptide directly stimulates adiponectin expression by improving adipose mobilization.

Under normal physiological conditions, adiponectin exerts beneficial effects, such as anti-inflammatory and anti-atherosclerosis proper-

ties, decreased insulin resistance, and cardiovascular system protective effects [3], although during CHF, elevated adiponectin levels can be correlated with disease severity and a poor prognosis (e.g. decompensated heart failure). It is possible that adiponectin also plays a role as a cachexia marker during the process of heart failure [16]. Supplying exogenous adiponectin may improve the condition of adiponectin resistance, and it may also provide a novel strategy for the treatment of heart failure.

### Study limitations

We recognize a few limitations in our study. First, this study was mainly cross-sectional with reduced statistical power/significance when considering the follow-up data, largely due to the low numbers of events accrued. This type of analysis only allowed for the detection of associations. Due to the study design, predictions and causal inferences could not be determined. Second, although differences in magnitude were identified with the current number of subjects, fulfilling the original hypotheses, the sample size in our study was still relatively small. A larger prospective study is warranted to confirm the predictive roles of CHF-related proteins. Third, despite being statistically significant, the magnitudes of the associations found (the slope of the relationship in regression analyses) were relatively small, and interactions between variables were not measured, although they may have occurred. Fourth, all CHF patients studied were Chinese. Therefore, it remains uncertain whether these results are fully applicable to other ethnicities. However, the identification of a new marker, with additional possible pathogenetic relevance, has to be regarded as a novelty in the area.

### Conclusions

Increased serum APN levels can be related to the severity of CHF. SAS can ultimately intensify the disease process and increase serum CTRP1 levels in CHF patients. However, such associations require additional investigation to better understand the role of SAS in CHF and to identify new targets/therapeutics to improve the outlook of CHF.

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### Disclosure of conflict of interest

None.

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