Introduction

Adiponectin (APN) is one of the circulating adipocytokines mainly produced by adipose tissue, and plays an important role in regulating insulin sensitivity, lipid metabolism, and systemic inflammation [1,2]. Circulating APN exists in blood in several multimeric forms. Recent studies have suggested that high molecular weight APN (HMW-APN) is the active form of this hormone and that the HMW-APN level or the ratio of HMW-APN to total APN (HMWR) are the superior predictors of metabolic abnormalities compared with total APN [3].

Heart failure (HF) is a complex syndrome with a high mortality that involves hemodynamic, neurohormonal, and metabolic abnormalities [4]. Recent studies have demonstrated that plasma total APN and HMW-APN levels increased in patients with chronic HF, and the elevated plasma APN levels identified patients with increased risk of dying, although the underlying mechanisms have remained unclear [5–7]. Since APN is believed to be beneficial for both hypertrophic and failing hearts [8,9], the elevated plasma APN levels may be a compensatory response to HF. However, how plasma total APN, HMW-APN, and HMWR respond to acute HF and after its treatment are not known.

Therefore, we designed a prospective observational study to investigate the changes in plasma total APN, HMW-APN levels, and HMWR during the course of acute HF, along with the hemodynamic, neurohormonal, and metabolic parameters and the clinical outcome.

Methods

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the ethics committee of the National Cerebral and Cardiovascular Center. Written informed consent was obtained from each subject before participation in this study.

Subjects

From February 2006 to July 2007, 20 consecutive patients admitted with acute non-ischemic and non-valvular HF were enrolled. Blood was sampled before the onset of any treatment and at discharge. The median and interquartile range of the time interval between the two blood sampling was 45 (21–70) days. The attending physicians treated the patients according to the guidelines for the management of acute HF issued by either the Japanese Circulation Society [10] or the European Society of Cardiology [11]. Ten patients admitted for the treatment of supraventricular arrhythmia without organic heart disease (8 men, aged 45 ± 13 years) were included as the control.

Assays

The plasma concentration of total APN was measured with a specific immunoradiometric assay [12]. Plasma HMW-APN levels were measured with a sandwich enzyme-linked immunoassay (ELISA) that employed a monoclonal antibody for human HMW-APN (Fujirebio ELISA kit, Tokyo, Japan) [13].

The plasma B-type natriuretic peptide (BNP) level was measured with a specific immunoradiometric assay kit for human BNP measurements (Shionoria; Shionogi Co., Ltd., Osaka, Japan) [14]. The insulin resistance index was determined by the homeostasis model assessment of insulin resistance (HOMA-R) method and calculated as the product of the fasting glucose (mg/dL) and fasting plasma insulin level (μU/mL) divided by 405 [15].

Echocardiography

Most of the echocardiograms were performed at the same day of the blood sampling but some of them were performed when the clinical status was stabilized. The median and interquartile range of the interval between the echocardiogram and the blood sampling was 0 (0–6) days. The left atrial diameter, left ventricular end-diastolic and end-systolic dimensions, left ventricular fractional shortening, and left ventricular septal thickness, and posterior wall thickness were determined by M-mode echocardiography. Echocardiograms were read by physicians who were blinded to any clinical information about the subjects. The left ventricular mass was calculated with the parameters measured by M-mode echocardiography [16]. Indexed values were obtained by dividing each parameter by the body surface area which was calculated according to the method of Mosteller [17]. Trans-mitral inflow profile was assessed in the apical four-chamber view by pulsed-wave Doppler echocardiography, with the Doppler beam parallel to the direction of the flow and the sample volume set at the tips of the leaflets. The peak velocity of early diastolic transmitral flow, the peak velocity of late diastolic transmitral flow, and the early diastolic transmitral flow deceleration time were measured [18]. Pulse wave tissue Doppler imaging was performed in the apical four-chamber view to acquire early diastolic mitral annular velocities [18]. The mean value of the septal and lateral values was used.

Follow up

After discharge from the hospital, the occurrence of clinical events was assessed by chart review or telephone interview. All cause death and the admission for worsening of HF were determined as clinical events.

Statistics

Numerical data are reported as either the mean $\pm$ SD or the median and interquartile range, as appropriate. The numerical values at admission and at discharge were compared by the paired t-test or Wilcoxon's matched pairs signed rank test, as appropriate. The categorical values at admission and at discharge were compared by McNemar test. For comparing the values at admission or at discharge with the values of control, Mann–Whitney test was performed. To avoid a type I error, a probability (p) value < 0.025 was considered as significant in this analysis. In the other all analyses, $p < 0.05$ was accepted as indicating statistical significance. The predictors of the plasma total APN and HMW-APN values at admission and at discharge were analyzed with simple

linear regression analysis using the selected variables known to relate with APN values in the previous reports. Variables are log-transformed as appropriate. For an exploratory survival analysis, patients were divided into two groups based on the median values of total APN, HMW-APN, and HMWR at admission and discharge and their changes. Then Kaplan—Meier survival curves were constructed for each of the subgroups and compared by log-rank test. The SPSS software package (16.0.2J; SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

Patient background

The baseline clinical, biochemical, and echocardiographic data are summarized in Table 1. None of the patients took either pioglitazone or fibrates, which can alter the plasma APN levels. Our patients had mostly dilated left ventricle and reduced systolic function. The results of transmitral flow showed that they had mostly severely compromised diastolic function. The majority of the patients were treated with diuretics or vasodilators. A minority of the patients needed positive inotropic agents. None of the patients received non-invasive positive pressure ventilation or endotracheal intubation.

Changes in plasma total APN, HMW-APN, and HMWR values and other variables

The plasma total APN, HMW-APN, and HMWR values at admission were 20.8 (14.5—38.9) μg/mL, 12.4 (7.7—23.3) μg/mL, and 0.60 (0.50—0.69), respectively (Table 2). The plasma total APN and HMW-APN values at admission were significantly higher than those of controls. Plasma total APN, HMW-APN, and HMWR values at discharge were 19.4 (7.2—27.3) μg/mL, 10.5 (3.2—12.8) μg/mL, and 0.52 (0.46—0.57), respectively, all of which were significantly decreased compared with the admission levels (Table 2 and Fig. 1). The plasma total APN value did not decrease to the degree of the controls.

Other variables also changed along with the treatment of HF (Tables 1 and 2). The body weight decreased by 6 kg. The BNP level was 677 (481—1206) pg/mL at admission and decreased to 212 (116—422) pg/mL at discharge. C-reactive protein levels, fasting glucose levels, and HOMA-R decreased. On the other hand, total cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol levels increased.

Predictors of the total APN and HMW-APN

The plasma total APN levels at admission were positively related with age, but not with other factors known to relate with APN in previous reports, such as body weight, BNP, or HDL cholesterol (Table 3) [2,12,19—22]. On the other hand, the plasma total APN levels at discharge positively related with BNP and HDL cholesterol levels as well as age, and negatively related with mean blood pressure. Other factors known to relate with plasma APN in previous studies, such
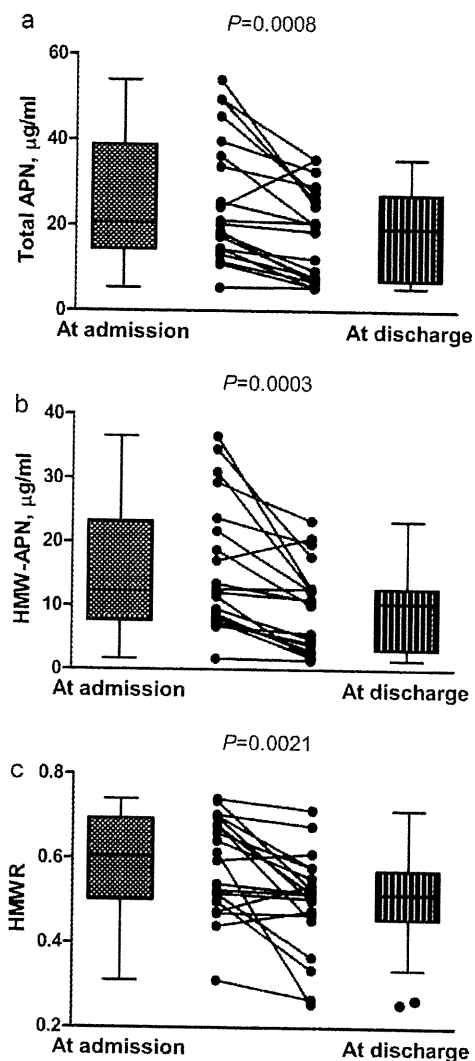

Figure 1   Changes of total adiponectin (APN) (a), high molecular weight APN (HMW-APN) (b), the ratio of HMW-APN to total APN (HMWR) (c) from admission to discharge.

as alanine aminotransferase, triglyceride, creatinine, C-reactive protein, and hemoglobin levels did not relate with the plasma total APN levels throughout the study [20—24]. The echocardiographic variables did not relate with the plasma total APN levels.

The plasma HMW-APN levels positively related with age at admission and positively related with HDL and age at discharge (Table 4). We could not identify a significant predictor of HMWR at admission. The log-transformed plasma total APN value was the only predictor of the HMWR at the discharge ($\beta = 0.25$, $p = 0.003$). Women are known to have higher total APN, HMW-APN, and HMWR [3,19], however, we could not find sexual difference neither at admission nor at discharge (data not shown).

Prognosis

The mean follow-up period after the index admission was 302 days (range: 67—584 days). After the discharge, 3

Table 1 Patient characteristics.

	At admission	At discharge
Age, year	63 ± 11	
Male gender, n (%)	17 (85)	
Etiology, n (%)		
Dilated cardiomyopathy	10 (50)	
Dilated phase hypertrophic cardiomyopathy	4 (20)	
Hypertensive heart disease	3 (15)	
Others	3 (15)	
Physical examination		
Height, cm	163.8 ± 8.5	
Weight, kg	66.7 ± 11.9	60.2 ± 11.1*
Body mass index, kg/m²	24.7 ± 3.3	22.3 ± 3.2*
Systolic blood pressure, mmHg	116 ± 17	110 ± 11
Diastolic blood pressure, mmHg	70 ± 14	64 ± 9
Mean blood pressure, mmHg	86 ± 13	79 ± 8
Heart rate, bpm	81 ± 22	67 ± 10*
NYHA functional class, n (%)		
II	6 (30)	
III	8 (40)	
IV	6 (30)	
Baseline medications, n (%)		
ACEI	7 (35)	10 (50)
ARB	9 (45)	8 (40)
Beta-blocker	13 (65)	19 (95)*
Diuretics	12 (60)	19 (95)*
Aldosterone blocker	5 (25)	13 (65)*
Digoxin	5 (25)	9 (45)
Nitrate	3 (15)	0 (0)
Oral inotropic agents	3 (15)	4 (20)
Acute phase treatment, n (%)		
Dopamine	1 (5)	
Dobutamine	5 (25)	
hANP	13 (65)	
Phosphodiesterase inhibitor	4 (20)	
Diuretics	13 (65)	
Laboratory examination		
AST, IU/L	31 (23−45)	26 (19−34)
ALT, IU/L	32 (19−51)	25 (15−45)
Total cholesterol, mg/dL	163 ± 36	194 ± 42*
Triglyceride, mg/dL	78 (66−115)	115 (96−148)*
HDL cholesterol, mg/dL	43 ± 10	50 ± 11*
Sodium, mEq/L	139 ± 3	138 ± 4
Blood urea nitrogen, mg/dL	21 ± 9	23 ± 12
Creatinine, mg/dL	1.0 ± 0.3	1.0 ± 0.3
Uric acid, mg/dL	7.5 ± 2.3	7.3 ± 2
C-reactive protein, mg/dL	0.45 (0.25−1.04)	0.12 (0.05−0.27)*
Fasting glucose, mg/dL	141 ± 48	104 ± 33*
Insulin, μU/mL	8.3 (5.9−15.0)	5.5 (3.8−13.6)
HOMA-R	2.5 (1.8−4.8)	1.3 (0.9−3.2)*
Hemoglobin, g/dL	13.0 ± 2.2	13.5 ± 2.3
Echocardiographic data		
Left ventricular end-diastolic diameter, mm	61 (53−69)	
Left ventricular end-systolic diameter, mm	52 (45−59)	
Fractional shortening, %	13 (12−19)	
Left atrial diameter, mm	53 (45−60)	
Interventricular septal wall thickness, mm	10 (7−11)	
Posterior wall thickness, mm	9 (8−11)	
Left ventricular mass, g	231 (204−281)	

Table 1 (*Continued*)

	At admission	At discharge
Left ventricular mass index, g/m^2	133 (117—176)	
E wave velocity, cm/s	86 (77—108)	
A wave velocity, cm/s	31 (22—36)	
E/A ratio	2.97 (2.19—3.93)	
Deceleration time, ms	130 (89—168)	
Mean Ea, cm/s	6 (5—7)	
Mean E/Ea ratio	16 (12—19)	

Continuous values are shown as median (interquartile range) or mean ± SD, as appropriate.

NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; hANP, human atrial natriuretic peptide; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment of insulin resistance; E, early diastolic transmitral flow; A, late diastolic transmitral flow; Ea, early diastolic mitral annular velocity.

* Significantly changed from admission to discharge ($p < 0.05$ with paired t-test, Wilcoxon's matched pairs signed rank test, or McNemar test as appropriate).

Table 2   Total APN, HMW-APN, and HMWR.

	Control (n = 10)	Heart failure (n = 20)		p*
		Admission	Discharge	
Total APN, μg/mL	7.1 (5.3—10.0)	20.8 (14.5—38.9)^I	19.4 (7.2—27.3)^I	0.0008
HMW-APN, μg/mL	3.8 (2.7—5.5)	12.4 (7.7—23.3)^I	10.5 (3.2—12.8)	0.0003
HMWR	0.52 (0.39—0.68)	0.61 (0.50—0.69)	0.52 (0.46—0.57)	0.0021
BNP, pg/mL	17 (6—27)	677 (481—1206)^I	212 (116—422)^I	0.0001

APN, adiponectin; HMW, high molecular weight; HMWR, HMW-APN ratio to total APN; BNP, B-type natriuretic peptide.
* Wilcoxon signed rank test comparing the values at admission and discharge.
^{I} $p < 0.025$ vs. control compared with Mann—Whitney test.

Table 3   Predictors of total APN.

	At admission		At discharge	
	β	p	β	p
Age	0.01	0.023	0.02	0.002
Weight	0.01	0.090	0.01	0.157
Mean blood pressure	0.00	0.539	−0.02	0.022
Log BNP	0.43	0.076	0.33	0.037
Log ALT	0.00	0.576	0.13	0.577
Log triglyceride	0.00	0.985	−0.59	0.132
HDL-cholesterol	0.01	0.068	0.02	0.003
Creatinine	0.12	0.566	0.19	0.467
HOMA-R	0.36	0.134	0.16	0.520
C-reactive protein	0.02	0.798	0.02	0.636
Hemoglobin	0.00	0.885	−0.03	0.303
Echocardiographic variables[a]				
Left ventricular end-diastolic diameter	0.00	0.584	0.03	0.889
Fractional shortening	−0.01	0.268	0.04	0.884
Left ventricular mass index	0.00	0.244	0.39	0.092
Mean E/Ea	0.00	0.832	−0.32	0.341

Dependant variable is log-transformed total APN.
APN, adiponectin; β, standardized coefficient; BNP, B-type natriuretic peptide; ALT, alanine aminotransferase; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment of insulin resistance; E, early diastolic transmitral flow; Ea, early diastolic mitral annular velocity.
[a] Echocardiographic variables are the values at admission.

Table 4   Predictors of HMW-APN.

	At admission		At discharge	
	β	p	β	p
Age	0.01	0.047	0.02	0.005
Weight	-0.01	0.142	-0.01	0.181
Mean blood pressure	0.00	0.557	-0.02	0.061
Log BNP	0.55	0.059	0.37	0.075
Log ALT	-0.15	0.491	0.45	0.315
Log triglyceride	-0.04	0.911	-0.71	0.153
HDL-cholesterol	0.01	0.119	0.02	0.004
Creatinine	0.22	0.371	0.33	0.323
HOMA-R	-0.40	0.092	0.17	0.494
C-reactive protein	0.04	0.653	0.04	0.567
Hemoglobin	-0.01	0.665	-0.05	0.175
Echocardiographic variables[a]				
Left ventricular end-diastolic diameter	0.00	0.503	0.11	0.650
Fractional shortening	-0.01	0.217	0.07	0.782
Left ventricular mass index	0.00	0.371	0.42	0.068
Mean E/Ea	0.00	0.986	-0.50	0.120

Dependent variable is log-transformed HMW-APN.

HMW-APN, high molecular weight adiponectin; β, standardized coefficient; BNP, B-type natriuretic peptide; ALT, alanine aminotransferase; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment of insulin resistance; E, early diastolic transmitral flow; Ea, early diastolic mitral annular velocity.

[a] Echocardiographic variables are the values at admission.

patients died and 6 patients were readmitted for worsening of HF. Exploratory survival analysis was performed with the composite endpoint of cardiac death and readmission for worsening of HF. The total APN and HMW-APN levels at the time of admission or discharge had no significant impact on the prognosis (data not shown). A higher value of HMWR at admission but not at discharge was associated with a better prognosis (Fig. 2a). A larger decrease in HMWR from admission to discharge was associated with a better prognosis (Fig. 2b). The patients with a higher HMWR at admission had a larger decrease in HMWR in response to the treatment (Table 5). The patients with a larger decrease in HMWR tended to have a higher HMWR at admission and were more hypertrophic (Table 5).

Discussion

This prospective observational study showed that the plasma total APN and HMW-APN were elevated at admission for exacerbation of acute HF. The plasma total APN, HMW-APN levels, and HMWR decreased in response to treatment. Furthermore, the patients with the higher HMWR at admission and those with the larger decrease in HMWR in response to the treatment showed a better prognosis.

Our study clarified the how plasma APN levels changed in the course of acute HF, which is consistent with a previous study showing that the total APN levels decreased during acute HF treatment [25]. Our study showed that the HMW-APN levels and HMWR as well as total APN decreased following acute HF treatment.

The plasma APN levels in acute HF may be modulated differently from in chronic HF. The plasma APN level is known to relate with gender, age, blood pressure, triglyceride, HDL
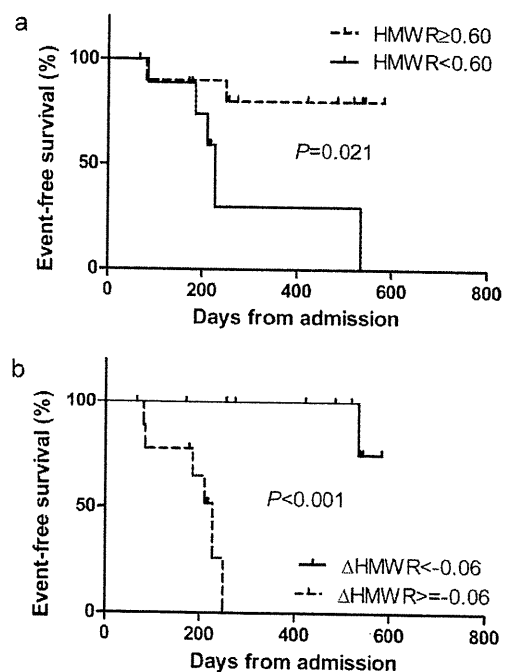

Figure 2   Kaplan–Meier event-free survival curves of groups divided by the ratio of high molecular weight adiponectin to total adiponectin (HMWR) at admission (a) and by the change of HMWR from admission to discharge (ΔHMWR) (b).

cholesterol, renal function, liver function, hemoglobin, C-reactive protein, and BNP [2,12,19–24]. In this cohort, the plasma APN levels did not relate with these conventional predictors of APN other than age. The plasma total APN at

Table 5 Patient background by HMWR at admission and ΔHMWR.

	HMWR ≥ 0.60	HMWR < 0.60	p	ΔHMWR < −0.06	ΔHMWR ≥ −0.06	p
Age, year	63 ± 10	63 ± 12	0.984	60 ± 14	66 ± 6	0.231
Male	90%	80%	1.000	80%	90%	1.000
Body weight at admission, kg	68 ± 13	65 ± 11	0.594	69.8 ± 11.6	63.5 ± 11.9	0.244
Body weight at discharge, kg	62 ± 12	59 ± 10	0.598	63 ± 11.3	57.4 ± 10.7	0.271
Δbody weight, kg	−7 ± 3	−6 ± 3	0.874	−6.9 ± 3.1	−6.1 ± 3	0.598
Total APN at admission, mg/mL	29.1 (16.9 to 46.6)	17.8 (14.2 to 28.2)	0.226	19.6 (13.9 to 46.6)	23.4 (14.2 to 37.2)	0.940
Total APN at discharge, mg/mL	26.23 (6.9 to 33.5)	10.86 (7.2 to 20.55)	0.112	13.2 (6.4 to 29.7)	20.3 (9.1 to 26.9)	0.597
Δtotal APN, mg/mL	−6.1 (−14.9 to −3.8)	−6.9 (−11.3 to −1.8)	0.821	−9.5 (−14.9 to −3.8)	−5.1 (−10.5 to −1.8)	0.364
HMW-APN at admission, mg/mL	20.45 (10.65 to 31.9)	9.1 (7.1 to 14.15)	0.028	12.5 (8 to 31.9)	12.4 (7.1 to 22.3)	0.545
HMW-APN at discharge, mg/mL	12.7 (3.68 to 20)	5.3 (2.45 to 11.35)	0.082	7.4 (2.5 to 14.1)	10.6 (4.7 to 14.5)	0.545
ΔHMW-APN, mg/mL	−5.6 (−17.2 to −3.3)	−3.8 (−6.7 to −0.9)	0.199	−5.9 (−17.2 to −3.3)	−3.5 (−6.7 to −0.9)	0.112
HMWR at admission	0.69 (0.66 to 0.71)	0.51 (0.46 to 0.53)	<0.001	0.67 (0.59 to 0.7)	0.52 (0.46 to 0.62)	0.082
HMWR at discharge	0.54 (0.49 to 0.6)	0.49 (0.36 to 0.52)	0.131	0.51 (0.36 to 0.56)	0.52 (0.47 to 0.63)	0.364
ΔHMWR	−0.141 (−0.212 to −0.068)	−0.011 (−0.071 to 0.021)	0.005	−0.16 (−0.21 to −0.11)	−0.01 (−0.03 to 0.02)	<0.001
BNP at admission, pg/mL	853 (637 to 1320)	538 (396 to 1114)	0.226	707 (445 to 1083)	677 (502 to 1538)	0.650
BNP at discharge, pg/mL	160 (99 to 893)	278 (123 to 395)	0.705	160 (99 to 532)	270 (123 to 372)	0.650
ΔBNP, pg/mL	−516 (−679 to −190)	−445 (−902 to −67)	0.650	−516 (−679 to −139)	−445 (−902 to −172)	0.821
Fractional shortening, %	13 (12 to 17)	15 (11 to 21)	0.326	12 (10 to 17)	15 (13 to 21)	0.070
Left ventricular mass index, g/m²	131 (109 to 152)	147 (117 to 189)	0.364	124 (97 to 137)	161 (125 to 189)	0.019

APN, adiponectin; HMW, high molecular weight; HMWR, HMW-APN ratio to total APN; BNP, B-type natriuretic peptide.

admission showed a borderline positive correlation with BNP ($\beta = 0.43$, $p = 0.076$); however, they related with BNP and HDL as well as age at discharge. The plasma HMW-APN levels positively related only with age at admission; however they positively related with HDL and age at discharge. A relationship between APN and BNP has been demonstrated in a wide range of patients [6,7,20,25—30], and it has been shown that BNP directly increased APN production in adipocytes [31]. However, the small number of patients in our study precluded showing a clear relationship between BNP and APN in the acute phase. Invasive monitoring of hemodynamics was not performed in this study. However, APN values did not associate with the ratio of early diastolic transmitral flow velocity to mitral annular velocity, which is known to relate with the left ventricular end-diastolic pressure.

We found the higher the HMWR at admission and the larger decrease in HMWR was associated with a preferable prognosis on the exploratory survival analyses. The decrease in HMWR may reflect the treatment responsiveness of patients with acute HF. Patients with a larger decrease in HMWR had a lower left ventricular mass index, which may indicate that they had less severe left ventricular remodeling. The cardioprotective effect of APN via several cellular pathways may mediate this better prognosis [8,9,32—34].

Our prognostic results may contradict several previous studies. Several studies in chronic HF have shown that higher APN levels were associated with a worse prognosis or future deterioration of cardiac function [5—7,25,26,35]. Tsutamoto et al. showed that higher total APN levels were associated with higher mortality in chronic HF; however, HMW-APN levels were less useful to predict mortality and HMWR levels were not different between survivors and non-survivors [7]. HMW-APN may lose its functional predominance and its predictive value under specific pathophysiological conditions [36]. In chronic HF, the relevance of increased plasma APN levels as an indicator of disease severity may be more relevant than its function as a pathophysiological mediator. Our study suggested that in acute HF higher levels of HMWR and their changes may exert their predominant cardioprotective effect and be better prognostic indicators in contrast to chronic HF. Dieplinger et al. showed that the higher plasma total APN level in acute HF related to a worse prognosis; however, they did not evaluate the levels of HMW-APN [37]. Because the HMWR values varied substantially even among subjects with similar total APN levels in plasma, we have to evaluate HMW-APN and HMWR levels in the future studies on acute HF [3].

Limitations

The small number of patients means that this study lacks a statistical power to conduct a complex analysis. However, the elevation of the plasma total APN and HMW-APN levels at admission and the decrease of these values and HMWR in response to treatment were evident even in this small number of patients.

Our patients did not show marked hypertension at the acute phase. Most of the patients could be classified as having acute HF with normal or moderately elevated blood pressure rather than with elevated blood pressure [38]. The former is predominantly accompanied with systemic congestion and minimal pulmonary congestion, whereas the latter is predominantly accompanied with pulmonary congestion, more often accompanied with preserved ejection fraction and thought to be caused by abnormal blood pressure responses [39]. Our cases might have fewer symptoms related with pulmonary congestion. Although 30% of the cases were classified as New York Heart Association class II, the relative paucity of symptoms does not necessarily mean they had less severe heart failure. In fact, about half of the patients had died or were readmitted during the follow-up period. Our patients may not include most severe patients in terms of the BNP values. The results of our study should be confirmed in a wider range of patients in future studies.

Our control subjects were not completely normal. They were admitted for the treatment of supraventricular arrhythmia. They were free from symptoms of heart failure with normal range of BNP and their plasma APN levels were similar to the values of normal subjects in the previous report [13,20].

Conclusion and clinical implication

Plasma total APN and HMW-APN levels are elevated in patients with acute HF. Total APN, HMW-APN levels, and HMWR decrease in response to the treatment. The higher HMWR at admission and larger decrease in HMWR may predict a better prognosis of acute HF. Further study is warranted to evaluate the prognostic impact of the dynamic response of APN in acute HF.

Acknowledgments

References

[1] Matsuzawa Y, Funahashi T, Nakamura T. Molecular mechanism of metabolic syndrome X: contribution of adipocytokines adipocyte-derived bioactive substances. Ann NY Acad Sci 1999;892:146—54.

[2] Santaniemi M, Kesaniemi YA, Ukkola O. Low plasma adiponectin concentration is an indicator of the metabolic syndrome. Eur J Endocrinol 2006;155:745—50.

[3] Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, Imai Y, Nagai R, Kadowaki T. Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. Diabetes Care 2006;29:1357—62.

[4] Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007—18.

[5] George J, Patal S, Wexler D, Sharabi Y, Peleg E, Kamari Y, Grossman E, Sheps D, Keren G, Roth A. Circulating adiponectin concentrations in patients with congestive heart failure. Heart 2006;92:1420–4.

[6] Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, Hildebrandt P. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. Circulation 2005;112:1756–62.

[7] Tsutamoto T, Tanaka T, Sakai H, Ishikawa C, Fujii M, Yamamoto T, Horie M. Total and high molecular weight adiponectin, haemodynamics, and mortality in patients with chronic heart failure. Eur Heart J 2007;28:1723–30.

[8] Liao Y, Takashima S, Maeda N, Ouchi N, Komamura K, Shimomura I, Hori M, Matsuzawa Y, Funahashi T, Kitakaze M. Exacerbation of heart failure in adiponectin-deficient mice due to impaired regulation of AMPK and glucose metabolism. Cardiovasc Res 2005;67:705–13.

[9] Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, Funahashi T, Ouchi N, Walsh K. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. Nat Med 2005;11:1096–103.

[10] Maruyama Y, Izumi T, Ogawa H, Kitakaze M, Takano T, Nakatani T, Hori M, Matsuda H, Momomura S. Guidelines for treatment of acute heart failure (JCS2006). Available at: http://www.j-circ.or.jp/guideline/pdf/JCS2006_maruyama_h.pdf. Accessed January 28; 2011.

[11] Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, Rhodes A, Swedberg K, Priori SG, Garcia MA, Blanc JJ, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:384–416.

[12] Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79–83.

[13] Nakano Y, Tajima S, Yoshimi A, Akiyama H, Tsushima M, Tanioka T, Negoro T, Tomita M, Tobe T. A novel enzyme-linked immunosorbent assay specific for high-molecular-weight adiponectin. J Lipid Res 2006;47:1572–82.

[14] Mukoyama M, Nakao K, Hosoda K, Suga S, Saito Y, Ogawa Y, Shirakami G, Jougasaki M, Obata K, Yasue H, Kambayashi Y, Inouye K, Imura H. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest 1991;87:1402–12.

[15] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.

[16] Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.

[17] Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.

[18] Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165–93.

[19] Nishizawa H, Shimomura I, Kishida K, Maeda N, Kuriyama H, Nagaretani H, Matsuda H, Kondo H, Furuyama N, Kihara S, Nakamura T, Tochino Y, Funahashi T, Matsuzawa Y. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. Diabetes 2002;51:2734–41.

[20] Ohara T, Kim J, Asakura M, Asanuma H, Nakatani S, Hashimura K, Kanzaki H, Funahashi T, Tomoike H, Kitakaze M. Plasma adiponectin is associated with plasma brain natriuretic peptide and cardiac function in healthy subjects. Hypertens Res 2008;31:825–31.

[21] Matsushita K, Yatsuya H, Tamakoshi K, Wada K, Otsuka R, Zhang H, Sugiura K, Kondo T, Murohara T, Toyoshima H. Inverse association between adiponectin and C-reactive protein in substantially healthy Japanese men. Atherosclerosis 2006;188:184–9.

[22] Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S, Malatino LS, Bonanno G, Seminara G, Rapisarda F, Fatuzzo P, Buemi M, Nicocia G, Tanaka S, Ouchi N, et al. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. J Am Soc Nephrol 2002;13:134–41.

[23] Matsubara M. Plasma adiponectin decrease in women with non-alcoholic fatty liver. Endocr J 2004;51:587–93.

[24] Matsubara M, Namioka K, Katayose S. Relationships between plasma adiponectin and blood cells, hepatopancreatic enzymes in women. Thromb Haemost 2004;91:360–6.

[25] Nakamura T, Funayama H, Kubo N, Yasu T, Kawakami M, Saito M, Momomura S, Ishikawa SE. Association of hyperadiponectinemia with severity of ventricular dysfunction in congestive heart failure. Circ J 2006;70:1557–62.

[26] Tamura T, Furukawa Y, Taniguchi R, Sato Y, Ono K, Horiuchi H, Nakagawa Y, Kita T, Kimura T. Serum adiponectin level as an independent predictor of mortality in patients with congestive heart failure. Circ J 2007;71:623–30.

[27] Pilz S, Mangge H, Wellnitz B, Seelhorst U, Winkelmann BR, Tiran B, Boehm BO, Marz W. Adiponectin and mortality in patients undergoing coronary angiography. J Clin Endocrinol Metab 2006;91:4277–86.

[28] von Eynatten M, Hamann A, Twardella D, Nawroth PP, Brenner H, Rothenbacher D. Relationship of adiponectin with markers of systemic inflammation, atherogenic dyslipidemia, and heart failure in patients with coronary heart disease. Clin Chem 2006;52:853–9.

[29] McEntegart MB, Awede B, Petrie MC, Sattar N, Dunn FG, MacFarlane NG, McMurray JJ. Increase in serum adiponectin concentration in patients with heart failure and cachexia: relationship with leptin, other cytokines, and B-type natriuretic peptide. Eur Heart J 2007;28:829–35.

[30] Haugen E, Furukawa Y, Isic A, Fu M. Increased adiponectin level in parallel with increased NT-pro BNP in patients with severe heart failure in the elderly: a hospital cohort study. Int J Cardiol 2008;125:216–9.

[31] Tsukamoto O, Fujita M, Kato M, Yamazaki S, Asano Y, Ogai A, Okazaki H, Asai M, Nagamachi Y, Maeda N, Shintani Y, Minamino T, Asakura M, Kishimoto I, Funahashi T, et al. Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. J Am Coll Cardiol 2009;53:2070–7.

[32] Takemura Y, Ouchi N, Shibata R, Aprahamian T, Kirber MT, Summer RS, Kihara S, Walsh K. Adiponectin modulates inflammatory reactions via calreticulin receptor-dependent clearance of early apoptotic bodies. J Clin Invest 2007;117:375–86.

[33] Shibata R, Izumiya Y, Sato K, Papanicolaou K, Kihara S, Colucci WS, Sam F, Ouchi N, Walsh K. Adiponectin protects against the development of systolic dysfunction following myocardial infarction. J Mol Cell Cardiol 2007;42:1065–74.

[34] Tao L, Gao E, Jiao X, Yuan Y, Li S, Christopher TA, Lopez BL, Koch W, Chan L, Goldstein BJ, Ma XL. Adiponectin cardioprotection after myocardial ischemia/reperfusion involves the reduction of oxidative/nitrative stress. Circulation 2007;115:1408–16.

[35] Kimura K, Miura S, Iwata A, Sugihara M, Arimura T, Nishikawa H, Kawamura A, Saku K. Association between cardiac function

and metabolic factors including adiponectin in patients with acute myocardial infarction. J Cardiol 2009;53:65—71.

[36] Kintscher U. Does adiponectin resistance exist in chronic heart failure? Eur Heart J 2007;28:1676—7.

[37] Dieplinger B, Gegenhuber A, Poelz W, Haltmayer M, Mueller T. Prognostic value of increased adiponectin plasma concentrations in patients with acute destabilized heart failure. Clin Biochem 2009;42:1190—3.

[38] Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol 2009;53:557—73.

[39] Mebazaa A, Gheorghiade M, Pina IL, Harjola VP, Hollenberg SM, Follath F, Rhodes A, Plaisance P, Roland E, Nieminen M, Komajda M, Parkhomenko A, Masip J, Zannad F, Filippatos G. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. Crit Care Med 2008;36:S129—39.