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Elevated Serum C-Reactive Protein Levels as a Predictive Indicator for Subsequent Renal Impairment in Patients with Acute Heart Failure

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Fukumoto, Y., Kishi, T., Tsutsui, H., Yamada, A., Okamatsu, S. and Takeshita, A. *Elevated Serum C-Reactive Protein Levels as a Predictive Indicator for Subsequent Renal Impairment in Patients with Acute Heart Failure*. Tohoku J. Exp. Med., 2007, **213** (4), 361-368 —— Renal impairment is often observed in acute heart failure (HF), which is an independent prognostic factor. It is important to identify high-risk patients, who need close follow-up and intensive care for renal protection. This study was conducted to identify the factors associated with the subsequent occurrence of HF-related renal dysfunction in patients, who were admitted to the hospitals due to acute HF symptoms. We evaluated 254 consecutive patients with acute HF. HF-related renal dysfunction was defined when highest serum creatinine level was greater than 1.2 mg/dl and the serum creatinine level increased by more than 50% compared with the baseline value during the admission. Forty patients with acute HF (16%) had subsequent renal dysfunction after admission. Elevated serum C-reactive protein (CRP) levels (≧ 5 mg/dl, odds ratio 2.51, $p = 0.008$ by univariate analysis, odds ratio 2.43, $p = 0.019$ by multivariate analysis) during the first week after admission and over-reduction of body weight (≧ 4.5 kg, odds ratio 2.68, $p = 0.005$ by univariate analysis, odds ratio 2.53, $p = 0.010$ by multivariate analysis) by acute HF treatment were significantly associated with this phenomenon. Patients with high CRP levels (≧ 5 mg/dl) during the first week after admission showed a significantly greater elevation of serum creatinine levels as compared to the levels before admission than those with low CRP levels (< 5 mg/dl). In conclsion, higher serum levels of CRP could predict the subsequent renal impairment in patients admitted with the worsening of HF symptoms. ———— acute heart failure; renal dysfunction; C-reactive protein; inflammation; infection

Acute heart failure (HF) is the common cardiovascular disease not only in North America and Europe (Gheorghiade et al. 2005a, b, 2006) but also in Japan (Tsuchihashi et al. 2000). Renal impairment is critical for patients with HF, because it is an independent prognostic risk factor

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(Fonarow et al. 2005; Fonarow and Heywood 2006; Lassus et al. 2007). Therefore, it is important to identify high-risk patients with acute HF who need close follow-up and intensive care for renal protection.

Renal function may be worsened by the reduced renal blood flow and glomerular filtration rate as a consequence of low cardiac output, the renal vasoconstriction due to increased sympathetic nervous system or the activated renin-angiotensin-aldosterone system, the increased peripheral vascular resistance, or over-use of loop diuretics such as furosemide (Schrier and Abraham 1999). However, little is known about the risk factors for HF-related worsening of renal function. In the present study, we examined the relationship between clinical factors and HF-related renal dysfunction. Recently, it has been reported that C-reactive protein (CRP) could be the predictors of readmission or mortality in patients with HF (Alonso-Martinez et al. 2002; Horwich et al. 2002). We thus included CRP levels as a potential risk factor in this analysis.

Methods

Study population

We retrospectively evaluated all 254 consecutive patients with acute HF caused by known cardiac structural and functional abnormalities, who admitted to Kyushu University Hospital from December 2002 to November 2003 and Aso-Iizuka Hospital from April 2004 to March 2005. There were 137 men and 117 women. We did not include patients who had acute HF due to acute coronary syndromes, those who have already taken hemodialysis, and those who died during the study. For each patient, we collected baseline demographics, clinical, procedural, and outcome data including the presence of infectious symptoms. We measured serum levels of creatinine, blood urea nitrogen (BUN), CRP, B-type natriuretic peptide (BNP), and lipid profiles during hospitalization. Serum biochemistry measurements including creatinine and CRP measurements were conducted by autoanalysis (TBA 200FR, Toshiba Medical Systems Corporation, Tokyo) with turbidimetric immunoassay.

Definitions

Acute heart failure was defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function. Cardiogenic shock was defined as clinical evidence of systemic hypoperfusion with less than 90 mmHg or the need for supportive measures to maintain systolic pressure more than 90 mmHg. We collected the data of serum creatinine levels at admission as the baseline values and defined patients with HF-related renal dysfunction when highest serum creatinine level during hospitalization was greater than 1.2 mg/dl and increased by more than 50% compared with the baseline values, as previously described (Fukumoto et al. 2003). We also measured body weight of patients during their hospitalization. We defined the body weight reduction as the reduction from the admission to the discharge. When multiple measurements of CRP were carried out in the first week of hospitalization, we regarded the highest CRP levels during the first week after admission and also evaluated the CRP levels at their discharge. High CRP levels of $\geqq$ 5 mg/dl during the first week after admission, those of $\geqq$ 0.5 mg/dl at their discharge, body weight reduction of $\geqq$ 4.5 kg, mean blood pressure of $\geqq$ 120 mmHg, heart rate of $\geqq$ 100 bpm, age of $\geqq$ 81 years old, and BNP levels of $\geqq$ 500 pg/m were defined as the top 1/3 percentile of this study population.

Data collection

Baseline demographic information (including age, sex, and body weight), New York Heart Association (NYHA) classes, presence of infection as a trigger of HF, vital signs, etiologies of HF (dilated cardiomyopathy (DCM), hypertensive heart disease (HHD), ischemic heart disease (IHD), valvular heart disease (VHD), and congenital heart disease), complications of coronary risk factors (diabetes mellitus, hypertension, chronic renal failure, and history of brain infarction) were recorded for each patient. Diabetes was defined as fasting blood sugar $\geqq$ 126 mg/dl or blood sugar during a 75 g oral glucose tolerance test $\geqq$ 200 mg/dl. Hypertension was defined as systolic blood pressure $\geqq$ 140 mmHg and/or diastolic blood pressure $\geqq$ 90 mmHg. Chronic renal failure was defined as creatinine clearance levels $\leqq$ 50 ml/min/m^2 calculated by Cockroft-Gault formula. Left ventricular ejection fraction (LVEF) was assessed by echocardiography. All patients were treated by diuretics such as furosemide and atrial natriuretic peptide (ANP), nitrate, catecholamine, phsphodiesterase (PDE) III inhibitor, and antibiotics if needed. The medications for HF (beta blocker, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or spirono-

lactone), aspirin, and statin (HMG-CoA reductase inhibitor) were recorded. Death and the need of hemodialysis or ventilation support during hospitalization were also recorded.

Statistical analysis

Continuous variables were expressed as mean ± S.D. Comparisons between patients with and without HF-related renal dysfunction were made by use of unpaired *t*-test for continuous variables and chi-square test for categorical variables, and logistic regression analysis for univariate and multivariate analyses to determine the independent predictors. All statistical analyses were performed using Stat View (SAS Institute, Cary, NC, USA) and Excel (Microsoft Corporation), and p values of less than 0.05 were considered statistically significant.

Results

HF-related renal dysfunction and CRP levels

No patient had cardiogenic shock, needed hemodialysis, and died in this study population. Baseline patients' characteristics were described in Table 1. Forty out of 254 patients (16%) had HF-related renal impairment by the definition mentioned above. There were no significant differences in age, sex, severity of heart failure, the etiologies, medications, baseline creatinine or BUN values, and lipid profiles between the patients with and without HF-related renal dysfunction (Table 2). However, univariate analysis indicated that patients with HF-related renal dysfunction had a significantly greater reduction in their body weight after acute HF treatment (–5.1 ± 3.3 vs –3.6 ± 3.5 kg, $p < 0.01$) and had significantly higher serum CRP levels during first week after admission (7.5 ± 6.7 vs 4.4 ± 5.7 mg/dl, $p < 0.01$), but not at discharge (0.9 ± 1.2 vs 0.7 ± 1.5 mg/dl, N.S), than those without HF-related renal dysfunction did (Table 2).

A univariate logistic regression analysis showed that both serum CRP levels of higher than 5 mg/dl and body weight reduction of greater than 4.5 kg by acute HF treatment were independent predictors of HF-related renal dysfunction (Table 3). There was a 2.51-fold increase in the risk of HF-related renal dysfunction in patients with high serum CRP levels (CRP ≧ 5 mg/dl) and a 2.68-fold increase in those with body weight

Table 1. Patient baseline characteristics.

	All patients (n = 254)
Age	75.9 ± 11.3
Gender (male/female)	137/117
NYHA class on admission	
II	102
III	118
IV	34
Infection as a trigger of HF	57 (22%)
BP (mmHg)	148 ± 34 / 81 ± 19
Heart rate (/min)	93 ± 26
EF (%)	49 ± 15
EF > 40%	183 (72%)
BNP (pg/ml)	581 ± 566
Etiology of HF	
DCM	32 (13%)
HHD	75 (30%)
IHD	94 (37%)
VHD	70 (28%)
Congenital	1 (0%)
Complication	
Diabetes mellitus	69 (27%)
Hypertension	161 (63%)
Chronic renal failure	173 (68%)
Brain infarction	21 (8%)
Baseline renal function	
Cr at admission	1.4 ± 1.1
Ccr (ml/min/m^2)	43.0 ± 27.8
BUN at admission	28 ± 18
Lipid profile	
TC (mg/dl)	169 ± 41
TG (mg/dl)	90 ± 57
LDL (mg/dl)	100 ± 34
HDL (mg/dl)	51 ± 19

Continuous data are shown as mean ± S.D. HF, heart failure; N, number; BP, blood pressure; EF, ejection fraction; BNP, B-type natriuretic peptide; DCM, dilated cardiomyopathy; HHD, hypertensive heart disease; IHD, ischemic heart disease; VHD, valvular heart disease; Cr, creatinine; Ccr, creatinine clearance; which is calculated by Cockroft-Gault formula; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein.

Table 2. Characteristics in patients with and without heart failure-related renal dysfunction.

	Heart failure-related renal dysfunction		*p* value
	No ($n = 214$)	Yes ($n = 40$)	
Age	75.9 ± 11.0	76.5 ± 13.0	N.S
Gender (male/female)	114/100	23/17	N.S
NYHA class on admission			
II	87	15	N.S
III	100	18	N.S
IV	27	7	N.S
Infection as a trigger of HF	45 (21%)	12 (30%)	N.S
BP (mmHg)	147 ± 34 / 80 ± 19	153 ± 37 / 83 ± 23	N.S
Heart rate (/min)	93 ± 26	92 ± 26	N.S
EF (%)	49 ± 16	50 ± 14	N.S
EF > 40%	153 (71%)	30 (75%)	N.S
BNP (pg/ml)	587 ± 583	464 ± 434	N.S
Body weight reduction (kg)	3.6 ± 3.5	5.1 ± 3.3	$p < 0.01$
Body weight reduction (≧ 4.5 kg)	68 (32%)	22 (55%)	$p < 0.01$
Etiology of HF			
DCM	29 (14%)	3 (8%)	N.S
HHD	62 (29%)	13 (33%)	N.S
IHD	75 (35%)	19 (48%)	N.S
VHD	69 (32%)	11 (28%)	N.S
Congenital	1 (0.5%)	0 (0%)	N.S
Complication			
Diabetes mellitus	57 (27%)	12 (30%)	N.S
Hypertension	137 (64%)	24 (60%)	N.S
Chronic renal failure	146 (68%)	27 (68%)	N.S
Brain infarction	17 (8%)	4 (10%)	N.S
Baseline renal function			
Cr at admission	1.4 ± 1.1	1.3 ± 0.7	N.S
Ccr (ml/min/m^2)	43.2 ± 28.2	42.3 ± 23.4	N.S
BUN at admission	29 ± 18	25 ± 16	N.S
CRP levels			
CRP ≧ 5 mg/dl, first week	70 (33%)	22 (55%)	$p < 0.01$
CRP ≧ 0.5 mg/dl at discharge	74 (35%)	18 (45%)	N.S
Lipid profile			
TC (mg/dl)	168 ± 42	174 ± 34	N.S
TG (mg/dl)	90 ± 59	87 ± 45	N.S
LDL (mg/dl)	99 ± 35	106 ± 30	N.S
HDL (mg/dl)	51 ± 20	51 ± 15	N.S

TABLE 2. Continue.

	Heart failure-related renal dysfunction		*p* value
	No ($n = 214$)	Yes ($n = 40$)	
Treatment during acute phase			
ANP	74 (35%)	14 (35%)	N.S
PDE III inhibitor	5 (2%)	1 (3%)	N.S
Furosemide	184 (86%)	37 (93%)	N.S
Nitrate	71 (33%)	13 (33%)	N.S
Catecholamine	14 (7%)	6 (15%)	N.S
Ventilation support	13 (6%)	5 (13%)	N.S
Antibiotics	27 (13%)	9 (23%)	N.S
Medications			
β blocker	136 (64%)	24 (60%)	N.S
ACEI/ARB	186 (87%)	37 (93%)	N.S
Statin	51 (24%)	11 (28%)	N.S
Aspirin	117 (55%)	25 (63%)	N.S
Spironolactone	91 (43%)	14 (35%)	N.S

Continuous data are shown as mean ± S.D. Comparisons between the two groups are made by use of unpaired *t*-test for continuous variables and chi-square test for categorical variables.

ANP, atrial natriuretic peptide; PDE, phosphodiesterase; ACEI/ARB, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker; CRP, C reactive protein.

TABLE 3. Univariate analysis of predictors for heart failure-related renal dysfunction using logistic regression analysis.

Variable	Odds ratio	95% Confidence interval	*p* value
Body weight reduction (≧ 4.5 kg)	2.68	1.35 – 5.33	0.005
CRP ≧ 5 mg/dl, first week	2.51	1.27 – 4.99	0.008
CRP ≧ 0.5 mg/dl at discharge	1.55	0.78 – 3.07	0.210
BNP ≧ 500 (pg/ml)	0.62	0.22 – 1.70	0.350
Age ≧ 81 (years old)	1.26	0.63 – 2.54	0.517
NYHA class II	0.88	0.44 – 1.76	0.709
NYHA class III	0.93	0.47 – 1.84	0.841
NYHA class IV	1.47	0.59 – 3.65	0.407
LVEF < 40 (%)	1.37	0.63 – 2.96	0.427
Use of furosemide	2.01	0.58 – 6.94	0.269
Mean BP ≧ 120 (mmHg)	1.61	0.76 – 3.41	0.215
Heart rate ≧ 100 (/min)	0.85	0.41 – 1.76	0.653

TABLE 4. Multivariate analysis of predictors for heart failure-related renal dysfunction using logistic regression analysis.

Variable	Odds ratio	95% Confidence interval	*p* value
Body weight reduction (≧ 4.5 kg)	2.53	1.25 – 5.13	0.010
CRP ≧ 5 mg/dl, first week	2.43	1.15 – 5.13	0.019
CRP ≧ 0.5 mg/dl at discharge	1.03	0.48 – 2.19	0.946
Use of furosemide	1.53	0.43 – 5.48	0.515

reduction (≧ 4.5 kg) after acute HF treatment (Table 3).

When all patients were divided into 2 groups by CRP levels of 5 mg/dl during the first week after admission, patients with higher CRP levels (≧ 5 mg/dl) showed the significantly greater elevation of serum creatinine levels as compared to the level before admission than those with lower CRP levels (< 5 mg/dl) (42.3 ± 45.2 vs 23.3 ± 26.7 mg/dl, $p < 0.01$).

A multiple logistic regression analysis showed that there was a 2.43-fold increase in the risk of HF-related renal dysfunction in patients with high serum CRP levels (CRP ≧ 5 mg/dl) and a 2.53-fold increase in those with body weight reduction (≧ 4.5 kg) after acute HF treatment (Table 4).

DISCUSSION

Acute HF is regulated by several factors including renin-aldosterone-angiotensin system, oxidative stress, and inflammatory responses. The present study has demonstrated that high CRP levels during the first week after admission can predict renal impairment in patients with acute HF. It has been reported that many cytokines and growth factors such as interleukin-4, interleukin-6, and tumor necrosis factor alpha, and adhesion molecules are upregulated in acute heart failure in parallel with circulating CRP levels (Andreassen et al. 1998; Sato et al. 1999; Deliargyris et al. 2000; Chin et al. 2003; Peschel et al. 2003). These inflammatory cytokines and growth factors can cause cytotoxic/nephrotoxic and vasoconstrictive responses (Fukumoto et al. 1997; Panzer et al. 2006), and may contribute to renal damages including apoptosis of mesangial cells and tubular injury (Duffield et al. 2000; Panzer et al. 2006; Zager et al. 2006). Therefore, inflammatory process seen in acute HF may be well recognized to induce renal impairment.

Furthermore, it also has been reported that CRP can directly decrease endothelial nitric oxide synthesis (eNOS) expression and bioactivity (Venugopal et al. 2002) and can reduce nitric oxide production (Verma et al. 2002). Elevated levels of CRP are also related with abnormal endothelial vascular reactivity in human (Gonzalez and Selwyn 2003), impaired acetylcholine-induced human forearm blood flow (Gonzalez and Selwyn 2003), or the progression of atherosclerosis in human and animals (Fukumoto et al. 2003; Ridker and Morrow 2003; Paul et al. 2004; Williams et al. 2004). Thus, high CRP levels from any cause may independently induce renal impairment by the reduction of renal blood flow and glomerular filtration rate.

Body weight reduction of more than 4.5 kg is also an independent predictor of HF-related renal dysfunction, as a greater body weight reduction reflects a greater dieuretics, which may worsen renal function in patients with acute HF (Schrier and Abraham 1999).

Acute HF and renal dysfunction coexist in the same patient, which is called the “cardiorenal syndrome”, and that renal impairment is an independent prognostic risk factor in acute HF (Fonarow et al. 2005; Fonarow and Heywood 2006; Lassus et al. 2007). It is considered that acute HF-related renal dysfunction is caused by not only diminished renal perfusion but also increased activity of the renin-angiotensin system,

oxidative stress, inflammation, and increased activity of the sympathetic nervous system (Bongartz et al. 2005). Further, renal dysfunction causes further congestion and neurohormonal activation, which are factors associated with adverse outcomes (Bongartz et al. 2005). While HF and renal dysfunction stimulate neurohormonal activation, increasing both preload and afterload and reducing cardiac output, inotropic agents further augment this neurohormonal activation. While diuretics can produce hypovolemia, intravenous vasodilators can cause hypotension, both of which can diminish renal perfusion (Fonarow and Heywood 2006). We need the delicate hemodymanic balance to manage such high-risk patients; however, few evidence-based data are available to guide management decisions (Fonarow and Heywood 2006). Therefore, further clinical studies are required to demonstrate how to avoid the HF-related renal dysfunction.

Limitations of the study

Several limitations should be mentioned for the present study. First, this is a retrospective study with a relatively small number of patients from the two institutions. Second, the mechanisms for renal impairment in patients with acute HF remain to be elucidated. Third, it was very difficult to see the peak of CRP levels and the initial onset of acute heart failure. Forth, it obviously remains to be examined what treatment can prevent the acute HF-related renal dysfunction, which should be examined in future.

Clinical implications and conclusion

Inflammation may worsen the renal function in patients with acute HF; therefore, anti-inflammatory therapies or renal vascular dilatations might be expected to be a novel therapeutic strategy to improve the prognosis of acute HF. ANP may be a promising therapeutic agent with renal protective effects, when it is used for long periods until CRP levels decline, although this deserves further investigation.

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