Table 7. Risk Factors for CR in Each Time Period

	IRR	*P* Value	95% CI	
Non-PPCI	Reference	n.a.	Reference	
PPCI conducted from 1977 to 1989	$6.21 \cdot 10^{-6}$	0.978	$4.1 \cdot 10^{-306}$	$9.4 \cdot 10^{296}$
PPCI conducted from 1990 to 2000	0.64	0.152	0.34	1.18
PPCI conducted from 2001 to 2011	0.25	<0.001	0.14	0.47
	IRR	*P* Value	95% CI	
No hypertension	Reference	n.a.	Reference	
Hypertensive from 1977 to 1989	5.61	<0.001	3.65	8.64
Hypertensive from 1990 to 2000	2.51	<0.001	1.59	3.95
Hypertensive from 2001 to 2011	1.25	0.387	0.76	2.06

The dummy variables from categories of the interaction term between time and PPCI were simultaneously included in the Poisson model. CR indicates cardiac rupture; IRR, incidence rate ratio; n.a., not available; PPCI, primary percutaneous coronary intervention.

These findings indicate that reperfusion therapy, especially PPCI, can prevent transmural progression of myocardial necrosis through early recanalization of the infarct-related artery.[9]

The present study showed that first MI, anterior infarct, female sex, and age >70 years remain significant risk factors for CR even in the most recent decade, consistent with previous findings.[3,10,11,22,23,25,26] High blood pressure could play an important role in the development of CR since it dramatically increases intracavitary pressures and shear stress force against the necrotic area during myocardial contraction, leading to a tear.[27] In fact, studies performed

Table 8. Characteristics of Autopsy Cases With CR (n=63)

	No reperfusion Tx (n=50)	Fibrinolysis (n=7)	PPCI (n=6)	*P* Value
Age*, y	71.5±8.8	73.1±5.8	74.7±7.0	0.639
Female, n (%)	26 (52.0)	3 (42.9)	1 (16.7)	0.253
Hypertension, n (%)	41 (82.0)	6 (85.7)	5 (83.3)	0.970
Diabetes or IGT, n (%)	13 (26.0)	3 (42.9)	3 (50.0)	0.356
Dyslipidemia, n (%)	6 (12.0)	2 (33.3)	1 (14.3)	0.356
Previous MI, n (%)	3 (6.0)	1 (14.3)	0 (0)	0.560
Time from symptom onset to admission >12 h, n (%)	26 (52.0)	1 (14.3)	1 (16.7)	0.078
Infarct location, n (%)				
Anterior	35 (70.0)	4 (57.1)	4 (66.7)	0.788
Inferior	11 (22.0)	3 (42.9)	2 (33.3)	0.443
Lateral	4 (8.0)	0 (0)	0 (0)	0.574
Other	0 (0)	0 (0)	0 (0)	
CABG, n (%)	3 (6.0)	0 (0)	1 (16.7)	0.459
Type of rupture, n (%)				
Free-wall rupture, acute	27 (54.0)	4 (57.1)	4 (66.7)	0.837
Free-wall rupture, subacute	7 (14.0)	1 (14.3)	1 (16.7)	0.985
Ventricular septal rupture	22 (44.0)	3 (42.9)	5 (83.3)	0.183

Free-wall rupture and ventricular septal rupture were observed together in 6 patients in the no-reperfusion-therapy group, 1 patient in the fibrinolysis group, and 5 patients in the PPCI group. CABG indicates coronary artery bypass; CR, cardiac rupture; IGT, impaired glucose tolerance; MI, myocardial infarction; grafting; PPCI, primary percutaneous coronary intervention; Tx, therapy.
*Mean±SD.

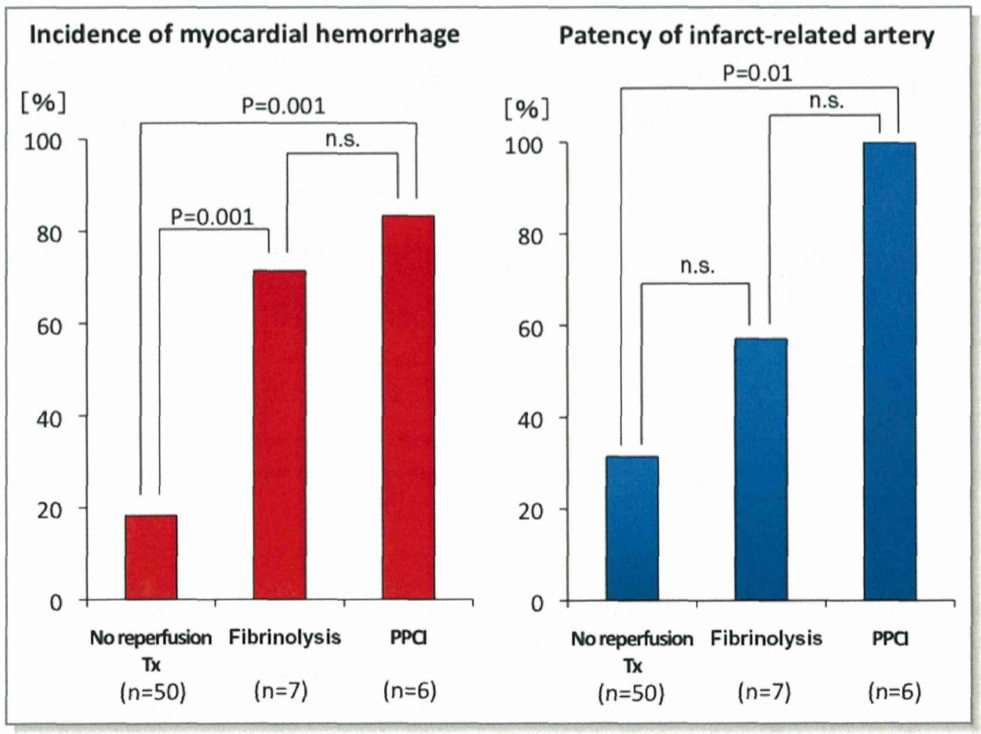

Figure 4. Increased incidence of myocardial hemorrhage is associated with an increased patency rate of infarct-related arteries based on autopsy data. The left panel shows the incidence rate of myocardial hemorrhage in the infarcted area. The right panel shows the patency rate of the infarct-related artery. Sixty-three autopsy patients with cardiac rupture were divided into the following 3 groups: no reperfusion therapy (Tx), reperfusion with fibrinolysis, and primary percutaneous coronary intervention (PPCI). n.s. indicates not significant.

several decades ago have reported an association between high blood pressure and an increased incidence of CR.[7,28–30] Importantly, along with other studies,[22,31,32] the present study also demonstrated that hypertension ceased to be significantly associated with CR in the most recent period. This finding may at least in part be due to changes in the definition of hypertension and the recommended post-AMI management of blood pressure (eg, β-blockers and angiotensin-converting enzyme inhibitors) during the past several decades.

High Incidence of Myocardial Hemorrhage in Patients With CR Undergoing Reperfusion Therapy Confirmed by Pathological Examination

To the best of our knowledge, this is the first study to analyze the association between pathological findings of CR and reperfusion therapy in patients with AMI. Before the reperfusion era, acute total occlusion of a coronary artery usually led to transmural myocardial necrosis and resulted in ventricular wall thinning or aneurysm formation.[33] In the present study, Becker type 3 rupture accompanied by wall thinning was the common type of CR in autopsy cases of patients who did not undergo reperfusion therapy. This finding is probably related to extensive myocardial necrosis. On the other hand, the proportion of Becker type 1 or 2 rupture was higher in patients with CR who underwent reperfusion therapy. The increase in the incidence of myocardial hemorrhage in patients who underwent reperfusion therapy, especially with a patent infarct-related artery (Figure 4), may be associated with an increased proportion of Becker type 1 or 2 rupture. Myocardial hemorrhage is a phenomenon that reflects severe microvascular damage and reperfusion injury following AMI.[34,35] Previous studies have demonstrated that myocardial hemorrhage could create dissections in the infarcted myocardium and delay the healing process.[36–39]

In a previous autopsy study,[40] 14 cases had undergone pharmacologic or combined forms of reperfusion therapy (13 streptokinase and 1 tissue-type plasminogen activator, including 4 with combined balloon angioplasty) and 5 had had purely mechanical therapy (balloon angioplasty). Hemorrhagic myocardial infarction was detected in all 14 patients who received pharmacologic or combined forms of reperfusion therapy, whereas it was not detected in any of the 5 patients who were treated with balloon angioplasty therapy alone. Similar findings of relatively minimal hemorrhagic injury

following direct angiography were observed in an experimental myocardial infarction model using right coronary artery occlusion in open-chest dogs.[41] An important finding of the present study was that reperfusion with both modalities resulted in a statistically higher incidence of myocardial hemorrhage associated with CR. The discrepancy between our autopsy study and previous ones may be related at least in part to the patency of the infarcted artery treated with coronary stents (Figure 4).[42–45] Indeed, recent studies using cardiac MRI showed that myocardial hemorrhage occurred in 25% to 40% of AMI patients undergoing PPCI and was associated with adverse left ventricular remodeling.[35,46] Thus, our data raise the possibility that in general PPCI reduces the incidence of CR, but in some cases it may induce reperfusion injury and myocardial hemorrhage, consequently accelerating Becker type 1 and 2 ruptures.

Perspectives on Preventing CR and Decreasing Associated Mortality in the Future

The natural history of CR is catastrophic, and medical treatment alone results in close to 100% mortality. Urgent surgical repair provides the best chance of survival in patients with CR.[10,47–49] The present study showed that the mortality rate of CR decreased to 50% with increasing use of emergent surgery. Over the years, the proportion of acute FWR decreased, while that of subacute FWR increased (Table 2). This finding may also be related to pathological observations. Reperfusion therapy has resulted in a pathological shift in CR type away from frank sudden rupture of a thinned free wall toward a slit-like rupture, which presents more subacutely and thus increases the possibility that surgical intervention can be attempted. At present, the most effective strategy for preventing CR following AMI is early revascularization by PPCI. However, the present pathological study also suggests a dark side to reperfusion therapy. CR patients undergoing PPCI have a higher prevalence of myocardial hemorrhage, which may be related in part to reperfusion injury. Thus, preventing reperfusion injury might be a novel target in future adjunctive treatment of AMI in order to achieve further reductions in the incidence of CR.

Limitations

The present study is a retrospective observational study. Therefore, some information that might affect the incidence of CR after AMI was unavailable or incomplete, such as the type (ST-segment or non–ST-segment elevation) of MI, cardiac enzyme levels, details on medical treatment before CR, and admission delays. Furthermore, data regarding the time from onset to reperfusion, which is important in terms of protecting the myocardium, were not available in all members of the AMI cohort. However, a prospective observational study could be difficult to perform because CR is rare in this era of reperfusion therapy. Although we conducted histological evaluations of autopsy cases in addition to our clinical review, the possibility of ascertainment bias or missing cases cannot be ruled out. In addition, it should be noted that our autopsy study results are based on a limited number of nonconsecutive patients.

Conclusions

Over the past several decades, the incidence of CR has decreased with the development of PPCI. However, first MI, anterior infarct, female sex, and age >70 years remain important risk factors for CR. Adjunctive cardioprotection against reperfusion injury is emerging in the current reperfusion era.

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Disclosures

None.

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Trends in the Clinical and Pathological Characteristics of Cardiac Rupture in Patients With Acute Myocardial Infarction Over 35 Years

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ORIGINAL ARTICLE

Impact of onset time of acute kidney injury on outcomes in patients with acute decompensated heart failure

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Abstract Since acute kidney injury (AKI) is not always related to mortality in patients with acute decompensated heart failure (ADHF), the aim of this study was to focus on onset time of AKI and its clinical importance. A total of 371 ADHF patients were included. The impact of AKI (≥0.3 mg/dl or 1.5-fold increase in serum creatinine level within 48 h) with early onset (≤4 days from admission) or late onset (≥5 days from admission) was assessed. AKI occurred in 99 patients, who were divided into two groups according to the median onset time of AKI: 50 with early onset of AKI and 49 with late onset of AKI. The maximum increase in serum creatinine level from admission was greater in patients with late onset of AKI than in patients with early onset of AKI ($p = 0.012$). Patients with late onset of AKI had a higher 12-month mortality rate than that in patients with early onset of AKI (log-rank test, $p = 0.014$). Late onset of AKI was an independent predictor of mortality (hazard ratio: 3.39, 95 % confidence interval: 1.84–6.18, $p < 0.001$). Late onset of AKI was associated with high blood urea nitrogen level at admission and intravenous administration of dobutamine. In conclusion, late onset of AKI related to high blood urea nitrogen level and intravenous administration of dobutamine, but not early onset of AKI, is linked to high mortality rate. Onset time of AKI may be useful for risk stratification of mortality in ADHF patients developing AKI.

Keywords Acute decompensated heart failure · Acute kidney injury · Onset time · Prognosis

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Introduction

Acute decompensated heart failure (ADHF) often leads to high rates of morbidity and mortality, and there is a need to determine the mechanisms for adverse outcomes. Attention has recently been paid to the interaction between the heart and kidney, termed cardiorenal syndrome, because of its association with adverse outcomes [1–3]. Several studies have suggested that worsening of renal function during ADHF therapy is one of the most powerful predictors of mortality [4–9]. However, after the exclusion of several biases, an increase in serum creatinine level has been shown to have little impact on mortality in patients with ADHF [10–15]. Aggressive diuresis due to high doses of diuretics, resulting in hemoconcentration, fluid loss, or substantial reduction in filling pressure, has been reported to be associated with an increased risk of worsening of renal function but linked to better clinical outcomes [10]. Taken together with the results of a recent study showing that an increase in serum creatinine level has an additive prognostic value only in patients with persistent congestion [11], these results suggest that an increase in serum creatinine level is not always related to the risk of mortality. It is necessary for physicians to focus on factors related to an increase in serum creatinine level to discuss the risk of mortality in patients with ADHF.

An increase in serum creatinine level has been found in patients with relief from congestion because of aggressive

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volume management, which often occurs in the early period of ADHF therapy. Thus, we hypothesized that an increase in serum creatinine level in the early period of ADHF therapy is linked to relief from congestion, not leading to high mortality rate, whereas an increase in serum creatinine level in the late period of ADHF therapy is linked to severe hemodynamic abnormalities, leading to high mortality rate. To test this hypothesis, we investigated onset time of acute kidney injury (AKI), defined as ≥0.3 mg/dl absolute or 1.5-fold increase in serum creatinine level within a time window of 48 h according to the AKI Network creatinine criteria [16], to determine the clinical importance of early or late onset of AKI in the pathophysiology and treatment of ADHF.

Methods

Study population

We retrospectively investigated 433 patients with ADHF admitted to the Cardiac Care Unit of the National Cerebral and Cardiovascular Center in Osaka, Japan between May 2006 and April 2009. ADHF was diagnosed on the basis of the European Society of Cardiology guidelines [17]. All patients had dyspnea at rest or with minimal activity and New York Heart Association functional class III or IV, and they required treatment with intravenous administration of diuretics. To assess the clinical importance of AKI caused exclusively by ADHF-related pathophysiology and treatment, we excluded patients who underwent procedures during ADHF therapy with a rise or remarkable change in serum creatinine level. Namely, we excluded patients who underwent cardiac surgery ($n = 8$), invasive procedures requiring contrast administration ($n = 23$), continuous renal replacement therapy (CRRT) on admission ($n = 4$), or intermittent renal replacement therapy since before admission ($n = 11$). Patients discharged within 48 h from admission due to non-cardiac complications were also excluded ($n = 6$) because of a lack of repeated measurements of serum creatinine level. This study was performed according to the principles of the Declaration of Helsinki and was approved by the institutional ethics committee (approved ID: M22-25). All patients provided written informed consent.

Clinical investigations

All patients were systematically characterized with regard to demographics, medical history, physical examinations, and medications during hospitalization. Intravenous administration of agents was judged on the basis of clinical indications by the treating physicians. Laboratory measurements were performed in all patients at admission. After admission, the timing of laboratory measurements was left to the discretion of the treating physicians.

To determine the clinical importance of onset time of AKI, we selected the definition of AKI suggested by the AKI Network creatinine criteria [16]. AKI was defined as ≥0.3 mg/dl absolute or 1.5-fold increase in serum creatinine level between the laboratory measurements within 48 h during ADHF therapy [16]. The values of serum creatinine level during ADHF therapy were selected, and the changes in serum creatinine level measured within 48 h were calculated, respectively. AKI was determined when the value of serum creatinine level increased ≥0.3 mg/dl absolute or 1.5-fold, compared with the value measured within 48 h last time.

Follow-up

The endpoint of the study was defined as all-cause mortality. Twelve-month follow-up was performed by clinical visits or telephone interviews with the patient, his or her relatives, or physicians. Independent investigators who had no role in patient follow-up and treatment obtained the information for outcomes.

Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. The differences in clinical characteristics were analyzed using the t test or Man–Whitney U test for continuous variables and the χ^2 test for categorical variables. The cumulative survival rates were estimated by Kaplan–Meier analysis, and the survival curves were compared by the log-rank test. The independent predictors of 12-month mortality were assessed by multivariate Cox proportional hazard analysis. Variables for univariate analysis included age, gender, systolic blood pressure, left ventricular ejection fraction, level of serum creatinine, blood urea nitrogen and plasma B-type natriuretic peptide at admission, early or late onset of AKI, and intravenous administration of dobutamine. Variables with $p < 0.10$ in the univariate analysis were entered into the multivariate analysis. Hazard ratios (HRs) are presented with 95 % confidence intervals (CIs). The factors related to early or late onset of AKI were determined by multivariate analysis. Variables for univariate analysis included age, gender, systolic blood pressure, level of serum creatinine, blood urea nitrogen and plasma B-type natriuretic peptide at admission, and intravenous administration of dobutamine. Variables with $p < 0.10$ in the univariate analysis were entered into the multivariate analysis. Odds ratios (ORs) are presented with 95 % CI. Statistical analysis was performed with JMP version 8.0

(SAS Institute Inc. Cary, NC, USA), and significance was defined as a value of $p < 0.05$.

Results

Study population

We identified 433 patients with ADHF. After exclusion based on the criteria, 381 patients remained. Ten patients were lost to 12-month follow-up, and the remained 371 patients constituted our study population. The mean age of patients was 73 ± 13 years, and 60 % of patients were male. Left ventricular ejection fraction was 36 ± 16 %. Serum creatinine level at admission was 1.23 ± 0.67 mg/dl.

Early or late onset of acute kidney injury

AKI occurred in 99 patients during ADHF therapy. To assess the incidence of AKI, the mean time interval of measurements of serum creatinine level within a time window of 48 h was 38 ± 10 h. The median onset time of AKI was 4.5 days. Patients were divided into two groups according to the median onset time: early onset of AKI (≤4 days from admission, $n = 50$) and late onset of AKI (≥5 days from admission, $n = 49$). Comparisons of clinical characteristics are shown in Table 1. Patients with late onset of AKI had lower systolic blood pressure and higher blood urea nitrogen level at admission, and were more frequently treated with intravenous administration of dobutamine.

Clinical outcomes

During ADHF therapy, the maximum increase in serum creatinine level from admission was greater in patients with late onset of AKI than in patients with early onset of AKI (early onset of AKI +0.79 ± 0.45 mg/dl vs. late onset of AKI +1.18 ± 0.97 mg/dl, $p = 0.012$). The increase in serum creatinine level from admission to discharge tended to be greater in patients with late onset of AKI than in patients with early onset of AKI (early onset of AKI −0.03 ± 0.75 mg/dl vs. late onset of AKI +0.29 ± 0.80 mg/dl, $p = 0.053$). The extent of decrease in body weight within 48 h, the time frame for the AKI Network creatinine criteria, was greater in patients with early onset of AKI than in patients with late onset of AKI (early onset of AKI −1.2 ± 1.6 kg vs. late onset of AKI −0.1 ± 1.1 kg, $p < 0.001$).

Overall, 55 patients died during the 12-month follow-up period, including 11 patients with early onset of AKI and 22 patients with late onset of AKI. Kaplan–Meier analysis revealed that patients with late onset of AKI had a higher 12-month mortality rate than that in patients with early onset of AKI (log-rank test, $p = 0.014$; Fig. 1). In multivariate Cox proportional hazard analysis, late onset of AKI (HR 3.39, 95 % CI 1.84–6.18, $p < 0.001$) and systolic blood pressure <100 mmHg (HR 2.51, 95 % CI 1.24–4.90, $p = 0.011$) were independent predictors of 12-month mortality, whereas early onset of AKI did not reach statistical significance (Table 2).

Table 1 Clinical characteristics

	Patients with early onset of AKI ($n = 50$)	Patients with late onset of AKI ($n = 49$)	p value
Age (years)	74 ± 12	75 ± 12	0.755
Male	28 (56 %)	33 (67 %)	0.250
Body mass index (kg/m^2)	23.1 ± 4.7	23.4 ± 4.0	0.725
Heart failure etiology			
Ischemic heart disease	17 (34 %)	23 (47 %)	0.193
Cardiomyopathy	8 (16 %)	6 (12 %)	0.596
Valvular heart disease	9 (18 %)	11 (22 %)	0.586
Hypertensive heart disease	9 (18 %)	6 (12 %)	0.430
Others	7 (14 %)	3 (6 %)	0.197
Rales (>1/2 lung fields)	19 (38 %)	17 (35 %)	0.854
Jugular venous distension	31 (62 %)	31 (63 %)	0.689
Peripheral edema	27 (54 %)	31 (63 %)	0.234
Systolic blood pressure (mmHg)	145 ± 38	126 ± 38	0.015
Diastolic blood pressure (mmHg)	83 ± 23	72 ± 23	0.022
Heart rate (beats/min)	100 ± 27	93 ± 26	0.200
Left ventricular ejection fraction (%)	35 ± 15	33 ± 15	0.785
Hemoglobin (g/dl)	11.1 ± 2.1	11.0 ± 2.1	0.858
Hematocrit (%)	33.0 ± 6.0	32.7 ± 6.4	0.782
Albumin (g/dl)	3.4 ± 0.5	3.5 ± 0.4	0.375
Sodium (mEq/l)	138 ± 5	136 ± 5	0.114
Blood urea nitrogen (mg/dl)	33 ± 18	42 ± 20	0.017
Creatinine (mg/dl)	1.73 ± 0.95	1.83 ± 0.86	0.559
Log B-type natriuretic peptide (pg/ml)	2.94 ± 0.41	3.00 ± 0.39	0.496
Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers	29 (58 %)	32 (65 %)	0.460
Beta-blockers	31 (62 %)	34 (69 %)	0.444
Aldosterone antagonists	21 (42 %)	24 (49 %)	0.491
Intravenous diuretics dose (mg)	418 ± 1191	444 ± 810	0.890
Intravenous dopamine	7 (14 %)	10 (20 %)	0.403
Intravenous dobutamine	13 (26 %)	22 (45 %)	0.049
Intravenous vasodilators	37 (74 %)	22 (65 %)	0.615

Data were expressed as mean ± standard deviation or numbers (%)

AKI acute kidney injury

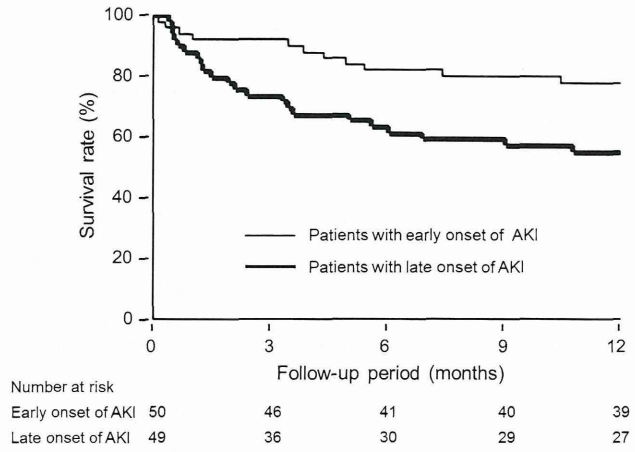

Fig. 1 Kaplan–Meier survival curves according to onset time of AKI. Log-rank test, $p = 0.014$. *AKI* acute kidney injury

Predictor of early or late onset of acute kidney injury

In multivariate analyses, early onset of AKI was independently associated with high serum creatinine level at admission (OR 3.58, 95 % CI 1.95–7.00, $p < 0.001$). Late onset of AKI was independently associated with high blood urea nitrogen level at admission (OR 4.69, 95 % CI 0.69–3.60, $p < 0.001$) and intravenous administration of dobutamine (OR 3.34, 95 % CI 1.62–6.88, $p = 0.002$) (Table 3).

Discussion

The major findings of the present study were that (1) patients with late onset of AKI had greater aggravation of renal function and higher mortality rate, (2) late onset of AKI, but not early onset of AKI, independently predicted mortality, (3) patients with early onset of AKI had greater decrease in body weight within 48 h than did patients with late onset of AKI, and (4) early onset of AKI was associated with high serum creatinine level at admission, and late onset of AKI was associated with high blood urea nitrogen level at admission and intravenous administration of dobutamine.

The present study demonstrated that early onset of AKI might be associated with basal renal dysfunction and strict fluid control. Early onset of AKI was not linked to high mortality rate, and serum creatinine level at discharge was almost the same as that at admission, suggesting that early onset of AKI has less impact on substantial renal dysfunction and adverse outcomes. Previous studies—showing that aggressive decongestion, even in the setting of worsening of renal function, can positively affect survival—support our results [10–15]. The kidneys in patients with chronic kidney disease have chronic hypoxia due to defective proliferation, rarefaction of renal microcirculation and interstitial fibrosis as a final common pathway independent of initial insults [18]. These renal morphological changes might promote an increase in serum creatinine level in the early period of ADHF therapy, consisting mainly of decongestion. However, more importantly, many of the increased serum creatinine level were reversible under the presumed renal morphological changes. With this knowledge, attending physicians might not hesitate to perform decongestion therapy in the early period of ADHF therapy.

Late onset of AKI was linked to adverse outcomes and related to high blood urea nitrogen and intravenous administration of dobutamine in the present study. Elevated blood urea nitrogen level has been reported to be an independent predictor of adverse outcomes in patients with heart failure [19–23]. Blood urea nitrogen level represents a surrogate marker for renal response to systemic hemodynamic changes related to pathophysiologic mechanisms of heart failure, such as an increase in arginine vasopressin release

Table 2 Univariate and multivariate analyses of predicting 12-month mortality

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95 % CI)	*p* value	Hazard ratio (95 % CI)	*p* value
Age >75 years	2.09 (1.21–3.76)	0.008	1.78 (0.99–3.27)	0.051
Male	1.09 (0.64–1.91)	0.749		
Systolic blood pressure <100 mmHg	3.99 (2.19–6.95)	<0.001	2.51 (1.24–4.90)	0.011
Left ventricular ejection fraction <35 %	1.53 (0.90–2.63)	0.117		
Blood urea nitrogen >24 mg/dl	3.25 (1.85–5.98)	<0.001	1.96 (0.97–4.04)	0.059
Creatinine >1.0 mg/dl	1.95 (1.14–3.44)	0.015	0.86 (0.45–1.69)	0.657
B-type natriuretic peptide >500 pg/ml	2.49 (1.34–5.07)	0.003	1.68 (0.87–3.49)	0.124
Early onset of AKI	1.70 (0.83–3.17)	0.136		
Late onset of AKI	5.79 (3.33–9.87)	<0.001	3.39 (1.84–6.18)	<0.001
Intravenous dobutamine	3.10 (1.77–5.31)	<0.001	1.51 (0.75–2.97)	0.245

AKI acute kidney injury, *CI* confidence intervals

Table 3 Univariate and multivariate analyses of factors related to late onset of AKI

	Univariate analysis		Multivariate analysis	
	Odds ratio (95 % CI)	*p* value	Odds ratio (95 % CI)	*p* value
Age >75 years	1.64 (0.89–3.07)	0.111		
Male	1.47 (0.79–2.84)	0.229		
Systolic blood pressure <100 mmHg	2.45 (1.11–5.12)	0.028	1.33 (0.53–3.13)	0.529
Blood urea nitrogen >24 mg/dl	6.74 (3.30–15.2)	<0.001	4.69 (2.00–11.9)	<0.001
Creatinine >1.0 mg/dl	3.81 (1.97–7.87)	<0.001	1.54 (0.69–3.60)	0.299
B-type natriuretic peptide >500 pg/ml	1.71 (0.89–3.47)	0.107	0.93 (0.44–2.01)	0.840
Intravenous dobutamine	4.77 (2.50–9.07)	<0.001	3.34 (1.62–6.88)	0.002

AKI acute kidney injury, *CI* confidence intervals

and hyperactivity of the renin-angiotensin-aldosterone system and sympathetic nervous system [24, 25]. They increase the reabsorption of blood urea nitrogen in the renal tubules, resulting in an increase in blood urea nitrogen level. In addition, the necessity for intravenous administration of dobutamine may reflect severe hemodynamic abnormalities. Right heart failure following low cardiac output and high pulmonary arterial/venous pressure causes persistent congestion including increased renal venous pressure. Increasing renal venous pressure induces hyperactivity of not only the intrarenal but also the systemic renin-angiotensin-aldosterone system and sympathetic nervous system, leading to a further fall in glomerular filtration rate. Thus, our results suggest that patients with late onset of AKI in the pathophysiology and treatment of ADHF had the above systems activated due to severe hemodynamic abnormalities, leading to permanent renal dysfunction and adverse outcomes.

The present study has clinical implications. The changes in serum creatinine level in the pathophysiology and treatment of ADHF often fluctuate dynamically, and their causes may be different at onset time. However, assessment of changes in serum creatinine level at multiple time points during ADHF therapy, as was done in the present study, was not performed in previous studies. Therefore, we investigated the clinical importance of early or late onset of AKI defined by the AKI Network creatinine criteria [16], and we found that late onset of AKI, but not early onset of AKI, was linked to high mortality rate. Early onset of AKI might be caused by basal renal dysfunction and strict fluid control, and late onset of AKI might be caused by severe hemodynamic abnormalities. The relationship of AKI with mortality in patients with ADHF has remained unclear [10–15], and the present study, therefore, adds one piece of evidence that onset time of AKI may be useful for risk stratification of mortality in ADHF patients developing AKI. Knowledge of the clinical differences in AKI would be valuable for attending physicians to make clinical decisions.

There are also limitations. First of all, the present study was a retrospective observational study in a single center. Our findings need to be confirmed in large multicenter trials. Secondly, the present study had a survival bias, since we defined early or late onset of AKI according to the median onset time of 4.5 days. Thirdly, since the timing of laboratory measurements during hospitalization was left to the discretion of the treating physicians, the time interval of measurements of serum creatinine level was not just 48 h, resulting in potential underestimation of the incidence of AKI. Fourthly, AKI defined by the AKI Network criteria [16] includes changes in serum creatinine level and urine output criteria, but we used only the serum creatinine criterion. Fifthly, we could not obtain data for evaluating the influence of accurate volume depletion. Sixthly, several studies suggest that AKI on admission is associated with adverse outcomes in patients with ADHF [26, 27]. In the present study, CRRT was started on the 1st day of admission in all 4 patients. The patients required CRRT might have AKI at the time of admission and adverse outcomes. However, these patients were excluded, because we could not judge them as AKI suggested by the AKI Network creatinine criteria [16]. Thus, we did not assess the effect of AKI which occurred until the 1st day of admission. Finally, direct hemodynamic parameters during ADHF therapy were not obtained.

Conclusions

Late onset of AKI, but not early onset of AKI, was linked to adverse outcomes in patients with ADHF. Early onset of AKI might be caused by basal renal dysfunction and strict volume control, and late onset of AKI might be caused by severe hemodynamic abnormalities. Our findings suggest the different mechanisms of early and late onset of AKI and the usefulness of onset time for risk stratification of AKI in patients with ADHF. Although clinical differences in AKI were found, specific therapy has not been established. Further studies are needed to improve clinical outcomes in ADHF patients developing AKI.

Conflict of interest This work was supported by the Program for Promotion of Fundamental Studies in Health Sciences of the Pharmaceuticals and Medical Devices Agency in Japan.