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ORIGINAL ARTICLE
Renal Disease

Admission Hyperglycemia Is an Independent Predictor of Acute Kidney Injury in Patients With Acute Myocardial Infarction

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Background: Acute kidney injury (AKI) and acute hyperglycemia are associated with unfavorable outcomes. The impact of acute hyperglycemia on the development of AKI after acute myocardial infarction (AMI), however, remains unclear. This study was undertaken to assess the relationship between admission glucose and incidence of AKI after AMI.

Methods and Results: This study consisted of 760 patients with AMI admitted to the National Cerebral and Cardiovascular Center within 48 h after symptom onset. Blood sample was obtained on admission and repeated sampling was done at least every 1 or 2 days during the first week. AKI was diagnosed as increase in serum creatinine ≥0.3 mg/dl or ≥50% within any 48 h. Ninety-six patients (13%) had AKI during hospitalization for AMI, and these patients had higher in-hospital mortality than those without AKI (25% vs. 3%, $P<0.001$). Patients with AKI had higher plasma glucose (PG) on admission than those without (222±105 mg/dl vs. 166±69 mg/dl, $P<0.001$). The incidence of AKI increased as admission PG rose: 7% with PG <120 mg/dl; 9% with PG 120–160 mg/dl; 11% with PG 160–200 mg/dl; and 28% with PG >200 mg/dl ($P<0.01$). On multivariate analysis admission PG was an independent predictor of AKI (odds ratio, 1.10; 95% confidence interval: 1.03–1.18, $P=0.02$).

Conclusions: Admission hyperglycemia might have contributed to the development of AKI in patients with AMI. (*Circ J* 2014; **78:** 1475–1480)

Key Words: Acute hyperglycemia; Acute kidney injury; Acute myocardial infarction

Acute kidney injury (AKI) is a complex disorder that occurs in a variety of conditions and is often associated with poor prognosis.[1–3] Acute myocardial infarction (AMI) is one of the critical conditions in which AKI is likely to occur, because of its comorbid factors, hemodynamic instability or other renotoxic agents.[4,5] Although it is often underrecognized, AKI is associated with adverse outcomes, including higher incidence of heart failure and mortality after AMI.[6] Despite the recent recognition of the importance of AKI, the incidence of AKI, factors contributing to AKI and its consequence in patients with AMI are not fully understood.

Editorial p 1329

Recent studies have demonstrated the prognostic importance of acute hyperglycemia in patients with AMI.[7–10] We have previously reported that high plasma glucose (PG) at the time of admission is linearly associated with increased in-hospital mortality in AMI patients. This finding is independent from a history of diabetes or hemoglobin A1c (HbA1c).[11,12] The postulated mechanisms for the causal relationship between acute hyperglycemia and poor outcome after AMI include enhanced oxidative stress, exacerbated inflammation, apoptosis, endothelial dysfunction and activation of coagulation and platelet activity.[13–16] Indeed, these are all factors that may exacerbate renal dysfunction in critical ill conditions and may cause AKI.[17]

In this study, we assessed the association between acute hyperglycemia and the development of AKI in patients with AMI.

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Table 1. Baseline AMI Patient Characteristics vs. Presence of AKI

	AKI (–)	AKI (+)	P-value
Demographics			
No. patients	664 (87)	96 (13)	
Age (years)	67.3±12.9	72.8±11.8	<0.001
Male	472 (71)	70 (73)	0.71
BMI	23.5±3.6	23.6±4.6	0.83
Medical history			
Hypertension	440 (66)	72 (75)	0.082
Dyslipidemia	375 (56)	40 (42)	0.006
Diabetes mellitus	204 (31)	51 (53)	<0.001
Current smoking	223 (34)	33 (34)	0.88
Previous angina	288 (43)	34 (35)	0.14
Previous MI	63 (9)	14 (15)	0.14
Previous PCI	71 (11)	17 (18)	0.057
Previous CABG	21 (3)	5 (5)	0.31
Diagnosis and management			
STEMI	544 (82)	81 (84)	0.55
Killip ≥2	110 (16)	52 (54)	<0.001
Emergency CAG	622 (94)	86 (90)	0.14
Primary PCI	577 (87)	77 (80)	0.091
Onset to admission (h)	7.6±10.1	6.6±8.4	0.37
Laboratory parameters			
Hemoglobin (g/dl)	13.6±2.1	12.2±2.6	<0.001
Creatinine (mg/dl)	1.0±1.2	1.8±1.8	<0.001
eGFR ($ml \cdot min^{-1} \cdot 1.73m^{-2}$)	70±24	46±27	<0.001
Admission plasma glucose (mg/dl)	166±69	222±105	<0.001
HbA1c (%); n=710	5.9±1.3	6.3±1.5	0.024
Treatment before admission			
Aspirin	129 (19)	26 (27)	0.081
ACEI and/or ARB	154 (23)	28 (29)	0.19
Calcium-channel blocker	177 (27)	29 (30)	0.46
β-blocker	73 (11)	11 (11)	0.89
Statins	121 (18)	22 (23)	0.27
Anti-hyperglycemic agent	91 (14)	26 (26)	0.0023

Data given as n (%) or mean±SD. ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAG, coronary angiography; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

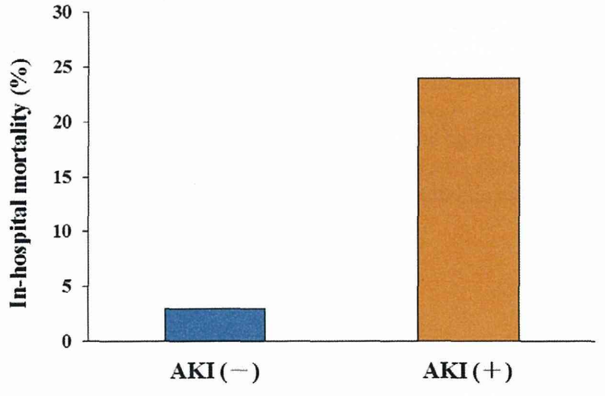

Figure 1. In-hospital mortality in patients with and without acute kidney injury (AKI) after acute myocardial infarction. The in-hospital mortality rate was significantly higher in patients with AKI than in patients without (25% vs. 3%; P<0.001).

Methods

Patients

From January 2007 to June 2012, 760 consecutive patients who were admitted to National Cerebral and Cardiovascular Center in Japan within 48 h after symptom onset were included into the retrospective observed registry of AMI at the National Cerebral and Cardiovascular Center. AMI was diagnosed on chest pain consistent with ongoing myocardial ischemia persisting >30 min and concomitant electrocardiographic changes. Serum creatine kinase was measured every 3–4 h for at least 24 h until it reached a peak, and the peak creatine kinase value had to be more than twice the normal upper limit.

Laboratory Data

Blood samples, including PG, creatinine and other baseline laboratory parameters were required to be obtained on admission. (Some parameters including HbA1c may be obtained days after admission.)

Blood sampling was repeated every 3–4 h until creatine

Table 2. Models of In-Hospital Mortality

	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Admission plasma glucose (per 18 mg/dl)	1.11 (1.01–1.18)	<0.001	1.04 (1.01–1.09)	<0.001
AKI	10.7 (5.67–20.6)	<0.001	3.5 (1.48–8.31)	0.004
Killip ≥2	24.9 (11.6–62.4)	<0.001	10.2 (4.2–28.1)	<0.001
eGFR (ml·min^{-1}·1.73 m^{-2})	0.96 (0.94–0.97)	<0.001	1.00 (0.99–1.02)	0.64
Hemoglobin (g/ml)	0.74 (0.65–0.84)	<0.001	0.87 (0.74–1.02)	0.091
Age (per 10 years)	1.03 (1.01–1.06)	0.0061	1.00 (0.97–1.04)	0.71
Diabetes mellitus	1.71 (0.92–3.15)	0.09	1.98 (0.85–4.88)	0.12
Previous PCI	4.05 (2.00–7.85)	0.002	2.27 (0.78–6.51)	0.13
Previous CABG	4.24 (1.36–11.1)	0.016	1.1 (0.23–4.37)	0.91
Aspirin	3.24 (1.72–6.04)	0.004	2.43 (0.91–6.37)	0.071

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

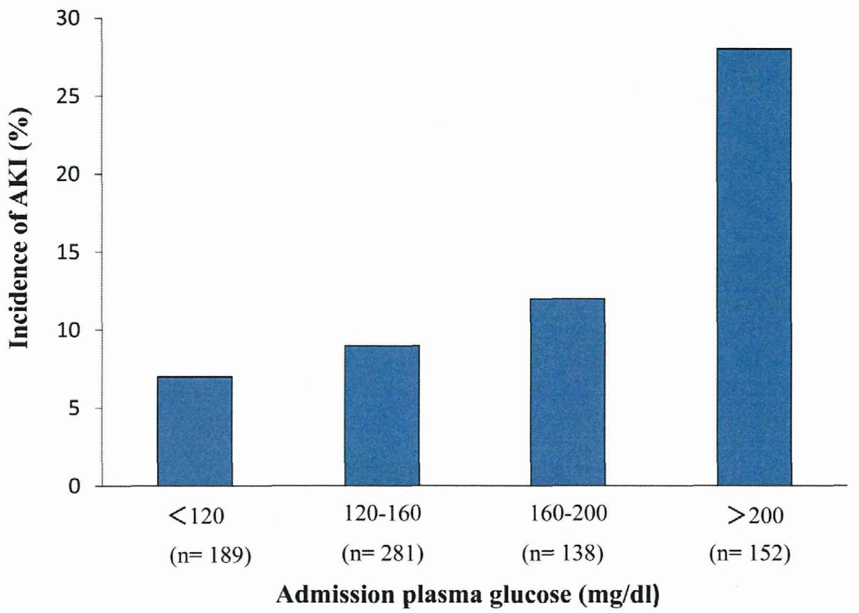

Figure 2. Incidence of acute kidney injury (AKI) in patients with acute myocardial infarction. The incidence of AKI increased as admission plasma glucose (PG) increased. There were 7% of 189 patients with PG <120 mg/dl; 9% of 281 patients with PG 120–160 mg/dl; 11% of 138 patients with PG 160–200 mg/dl; and 28% of 152 patients with PG >200 mg/dl (P<0.001).

kinase reached a peak. Creatinine was measured every day or every 2 days for at least 1 week after hospital admission during the first week. AKI was diagnosed according to criteria proposed by the AKI network, which defines AKI as an increase in serum creatinine ≥0.3 mg/dl or an increase ≥150% from baseline within any 48 h.[18]

Emergency coronary angiography was performed in most cases if indicated. Selective coronary angiography was performed in multiple projections before the initiation of reperfusion therapy. Immediately after diagnostic angiography, reperfusion therapy was performed mostly with primary percutaneous coronary intervention (PCI) with stent. The allocation of thrombolysis or coronary intervention was not randomized and was based on physician decision.

Data Analysis

In the current study, we investigated the prevalence of AKI and admission hyperglycemia. Impacts of AKI and admission hyperglycemia on in-hospital mortality were also assessed. Finally, we evaluated factors that are related to the development of AKI, especially impact of admission hyperglycemia on renal function.

Categorical data are reported as proportions and continuous data as mean±SD. Statistical analysis was done with the chi-squared test for categorical variables, and t-test was used for continuous variables. Logistic regression analysis was used to obtain odds ratios (OR) and 95% confidence intervals (CI) for the development of AKI. In multivariate analysis, the association between admission PG and the development AKI was adjusted for age, and all predictors of AKI. Because HbA1c was not obtained in 50 patients (6.5%), 2 models of multivariate analysis were used. In the first model, age, hypertension, dyslipidemia, diabetes mellitus, Killip class, hemoglobin, estimated glomerular filtration rate (eGFR), creatinine, previous angina, previous PCI, primary PCI and use of aspirin and anti-hyperglycemic agent were adjusted. In the second model, HbA1c was added to these variables. We used JMP (version 10.0, SAS institute). A significance level of 0.05 was used and 2-tailed tests were applied.

Table 3. Models of Incidence of AKI

	Univariate		Multivariate			
			Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Admission plasma glucose (per 18 mg/dl)	1.11 (1.00–1.21)	<0.001	1.18 (1.06–1.31)	0.002	1.10 (1.03–1.18)	0.02
Killip ≥2	5.95 (3.79–9.38)	<0.001	3.4 (1.97–5.86)	<0.001	3.49 (1.91–6.39)	<0.001
eGFR ($ml\cdot min^{-1}\cdot 1.73 m^{-2}$)	0.96 (0.95–0.97)	<0.001	0.97 (0.96–0.98)	<0.001	0.97 (0.96–0.98)	<0.001
Dyslipidemia	0.55 (0.35–0.84)	0.006	0.51 (0.27–0.77)	0.003	0.37 (0.21–0.66)	0.005
Anti-hyperglycemic agent	2.18 (1.30–3.59)	0.002	1.16 (0.55–2.43)	0.69	1.05 (0.46–2.39)	0.91
Diabetes mellitus	2.6 (1.66–3.95)	<0.001	1.8 (0.92–3.34)	0.08	1.58 (0.73–3.29)	0.23
Age (per 10 years)	1.03 (1.02–1.06)	<0.001	1.01 (0.99–1.03)	0.20	1.01 (0.99–1.04)	0.46
Hemoglobin (g/dl)	0.77 (0.70–0.85)	<0.001	0.93 (0.83–1.04)	0.23	0.86 (0.75–0.98)	0.27
Previous PCI	1.79 (0.98–3.14)	0.057	1.3 (0.56–2.91)	0.52	1.34 (0.52–3.33)	0.53
Emergency PCI	0.61 (0.36–1.08)	0.09	0.97 (0.47–1.91)	0.94	0.91 (0.40–1.92)	0.82
Aspirin	1.54 (0.93–2.49)	0.081	1.47 (0.73–3.06)	0.28	1.86 (0.85–4.28)	0.12
Hypertension	1.52 (0.94–2.53)	0.082	1.03 (0.57–1.92)	0.91	1.17 (0.61–2.34)	0.63
HbA1c (%)	1.18 (1.01–1.37)	0.024	–	–	1.05 (0.79–1.39)	0.73

HbA1c was not obtained in 50 patients (6.5%). Two models of multivariate analysis were used. In the first model, age, hypertension, dyslipidemia, diabetes mellitus, Killip class, hemoglobin, eGFR, creatinine, previous angina, previous PCI, primary PCI and use of aspirin and anti-hyperglycemic agent were adjusted. In the second model, HbA1c was added to these variables.
Abbreviations as in Tables 1,2.

Results

Incidence of AKI

Baseline characteristics of the study patients are listed in **Table 1**. Emergency coronary angiography was performed in 708 patients (93%) and primary PCI in 654 patients (86%). Among the entire 760 patients, AKI developed in 96 patients (13%). The demographic, clinical, and biochemical characteristics of the patients with and without AKI are listed in **Table 1**. There were significant differences in age, diabetes mellitus, Killip class ≥2, dyslipidemia, creatinine and eGFR, HbA1c, hemoglobin, and admission glucose between patients with AKI and those without. There was no significant difference in emergency coronary angiography and primary PCI. Anti-hyperglycemic agent (oral hyperglycemic drug and/or insulin) were more frequently used in patients with AKI before AMI (**Table 1**).

In-Hospital Mortality

In-hospital mortality of the entire patient group was 5.7%. In-hospital mortality was significantly higher in patients with AKI than in those without AKI (25% vs. 3%, P<0.001; **Figure 1**). On univariate analysis, admission PG, AKI, Killip class, eGFR, hemoglobin, age, diabetes mellitus, previous PCI, previous CABG and aspirin were associated with in-hospital mortality (**Table 2**). Multivariate analysis showed that both AKI and admission PG were independent predictors of in-hospital mortality.

Admission PG and AKI

Patients with AKI had higher PG on admission (222±105 mg/dl vs. 166±69 mg/dl, P<0.001). **Figure 2** shows the relationship between admission PG and the incidence of AKI. The incidence of AKI increased as admission PG increased. The incidence of AKI was 7% of 189 patients with PG <120 mg/dl; 9% of 281 patients with PG 120–160 mg/dl; 11% of 138 patients with PG 160–200 mg/dl; and 28% of 152 patients with PG >200 mg/dl (P<0.001; **Figure 2**).

On univariate logistic regression admission PG was associated with AKI, along with age, diabetes, dyslipidemia, Killip ≥2, eGFR, hemoglobin, HbA1c, and the use of anti-hyperglycemic drugs. After adjusting these variables, admission PG remained as an independent predictor of AKI in patients with AMI, but diabetes mellitus and HbA1c were not (**Table 3**).

Discussion

The major findings of this study are: (1) AKI developed in 13% after AMI; (2) AKI was associated with in-hospital mortality after AMI; and (3) admission hyperglycemia was an independent risk factor for AKI in patients with AMI.

Incidence of AKI in AMI Patients

In previous studies the incidence of AKI has ranged from 10% to 20% in AMI patients.[6,19,20] The ACTION registry, which enrolled 59,970 patients with AMI who were mostly treated with primary PCI, reported that 16.1% of patients developed AKI during hospitalization.[20] In the current study, the incidence of AKI was 13%, which is similar to these previous reports.

In the last decade, primary PCI has become the treatment of choice for patients with AMI, and number of patients who receive coronary angiography has been rapidly increasing. The contrast medium is nephrotoxic, and may cause acute tubular necrosis. This is termed 'contrast-induced AKI (CI-AKI)'.[5,21–23] There is a concern about the risk of CI-AKI for patients undergoing coronary angiography and primary PCI for AMI. In the present study, however, both emergency angiography and primary PCI were not associated with AKI in AMI patients. Consistent findings have been reported. Amin et al assessed the temporal trend in the use of PCI and the development of AKI in 31,532 patients with AMI. Interestingly, the incidence of AKI has progressively declined (from 26.6% in the year 2000 to 19.7% in 2008), as the use of PCI has progressively increased (from 32.1% in the year 2000 to 47% in 2008).[6] Therefore, CI-AKI seems not to be the main cause of AKI in patients with AMI.

AKI and In-Hospital Mortality

In the current study, the in-hospital mortality of patients with AKI was 8-fold as high as those without AKI. It has been well demonstrated that AKI is a strong predictor of mortality after AMI. In the ACTION registry, the in-hospital mortality increased as the stage of AKI advanced, and overall mortality in patients with AKI was 15%, which was 7.5-fold higher as compared to those without AKI (2%).[19]

Comorbid factors and the severely ill condition of patients with AKI are at least in part responsible for the higher mortality of these patients. Even after adjusting these factors, however, AKI remains as an independent predictor of mortality in AMI patients. Previous studies have suggested that AKI can affect the heart through several pathways.[24–26]

Predictors of AKI in AMI

Worsening of renal function may have negative effects on heart and circulation, resulting in higher mortality after AMI in patients with AKI.[27] In turn, a rapid worsening of cardiac function may lead to AKI. The concept of cardiorenal syndrome (CRS) has become widely accepted in recent years.[17,28] The latter condition, characterized by initiation and/or progression of renal insufficiency secondary to heart failure, is the most common type of CRS, but its mechanisms are multiple and complex.

Acute decline in renal function is not simply due to decreased renal blood flow; acceleration in cardiovascular pathobiology through activation of inflammatory pathways is considerably responsible for the development of AKI. In patients with AMI, neurohormonal, immunological and inflammatory pathways are activated, resulting in kidney injury.[28] Inflammatory biomarkers, including pentraxin 3, interleukin-1 and -6, tumor necrotic factor-α and so on, have been shown to be associated with AKI.[29–31]

Recently, several studies have focused on the importance of acute hyperglycemia as a determinant of outcome in patients with AMI. Elevation of PG on admission, acute hyperglycemia, is a common feature early after AMI, even in the absence of diabetes mellitus.[7,8,11,12] Numerous studies have described the association between acute hyperglycemia and adverse outcome in patients with AMI. Multiple physiological studies have shown that hyperglycemia has a direct detrimental effect on ischemic myocardium through several mechanisms, including oxidative stress, inflammation, apoptosis, endothelial dysfunction, hypercoagulation, and platelet aggregation.[14–16]

Brief episodes of antecedent myocardial ischemia have protective effects against subsequent prolonged ischemia, termed 'ischemic preconditioning'. Such effects are also generated by brief intermittent ischemia after the ischemic event (postconditioning) and observed even in remote organs (remote conditioning). A recent study has reported that remote post-conditioning prevents the development of AKI after PCI.[32] We have previously reported that admission hyperglycemia abolishes ischemic preconditioning.[33,34] It may also attenuate renoprotective effects of ischemic preconditioning in patients with AMI.

Previous clinical studies have reported that elevated PG is associated with worsening of renal function after cardiac surgery or coronary angiography.[21,35] In the current study, patients with elevated glucose on admission were at higher risk of death during hospitalization for AMI, regardless of the use of coronary angiography or primary PCI. Although it remains unknown whether hyperglycemia is causally related to deterioration of kidney function, the positive relationship between admission glucose and the development of AKI remained significant even after adjusting potential confounding factors, suggesting that hyperglycemia is not a simple surrogate marker of AKI.

Study Limitations

The present results should be interpreted in the context of several potential limitations. First, the present study was a single-center and retrospective study. We did not obtain sufficient data on contrast medium volume to analyze the relationship between volume of contrast medium and AKI. Second, the mechanisms by which acute hyperglycemia is correlated with AKI in AMI patients remained unclear. The relationship between acute hyperglycemia and systemic inflammatory responses, and the mechanisms of kidney injury following AMI should be analyzed in basic and clinical studies in the future.

Conclusions

Admission hyperglycemia could be an independent predictor for AKI in AMI patients. Careful monitoring of renal function should be done for patients with AMI and admission hyperglycemia.

Disclosures

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ORIGINAL ARTICLE

Extensive late gadolinium enhancement on cardiovascular magnetic resonance predicts adverse outcomes and lack of improvement in LV function after steroid therapy in cardiac sarcoidosis

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ABSTRACT

Background Gadolinium-enhanced cardiovascular magnetic resonance is an emerging tool for the diagnosis of cardiac sarcoidosis (CS); however, the correlations between extent of late gadolinium enhancement (LGE) and efficacy of steroid therapy and adverse outcomes in patients with CS remain unclear.

Objective We aimed to clarify the prognostic impact of extent of LGE in patients with CS.

Methods Before the start of steroid therapy, 43 consecutive LGE-positive patients with CS were divided into two groups based on the extent of LGE by a median value: small-extent LGE (LGE mass <20% of LV mass; n=21) and large-extent LGE (LGE mass ≥20% of LV mass; n=22). We examined the correlations between extent of LGE and outcomes after steroid therapy.

Results Among the 6 patients who died from heart disorders, 11 patients who were hospitalised because of heart failure and 6 patients who suffered life-threatening arrhythmia during the follow-up period, large-extent LGE predicted higher incidences of cardiac mortality and hospitalisation for heart failure. Multivariate Cox regression analysis showed that large-extent LGE was independently associated with combined adverse outcomes including cardiac death, hospitalisation for heart failure, and life-threatening arrhythmias. In the small-extent LGE group, LV end-diastolic volume index significantly decreased and LVEF significantly increased after steroid therapy, whereas in the large-extent LGE group, neither LV volume nor LVEF changed substantially.

Conclusions Large-extent LGE correlates with absence of LV functional improvement and high incidence of adverse outcomes in patients with CS after steroid therapy.

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder of unknown cause with symptomatic myocardial involvement in up to 7% of affected patients.[1–3] Although it is generally associated with a low mortality rate, concomitant cardiac involvement worsen its prognosis.[4 5] Therefore, detection of myocardial involvement is critical for management of patients with sarcoidosis. In patients with sarcoidosis, gadolinium-enhanced cardiovascular magnetic resonance (CMR) is a useful diagnostic tool to qualitatively detect myocardial involvement.[6–8] In most patients with cardiac sarcoidosis (CS), late gadolinium enhancement (LGE) is typically localised in the basal and lateral segments of the LV wall or epicardium, which does not fit any specific coronary perfusion area.[9] LGE in CMR has been reported to reflect myocardial fibrosis and granulomatous inflammation in patients with CS.[7] It has also been reported that the presence of myocardial LGE can predict adverse events in patients with systemic sarcoidosis.[7 10] However, the prognostic impact of the extent of LGE has not been fully investigated. In this study, we examined the correlations between the extent of LGE and adverse outcomes, as well as the efficacy of steroid therapy in patients with CS.

METHODS

Study patients

Medical records were screened to identify patients diagnosed with CS in our institution from May 2000 to May 2012. CS was diagnosed according to the guidelines of the Specific Diffuse Pulmonary Disease Research Group, Sarcoidosis Division (Japanese Ministry of Health and Welfare).[11] In brief, CS was diagnosed on the basis of histological findings or clinical findings. Histological diagnosis of CS was confirmed when histological analysis of endomyocardial biopsy specimens demonstrated epithelioid granuloma without caseating granulomas. Clinical diagnosis of CS was confirmed by the presence of an electrocardiographic (ECG) abnormality suggesting myocardial injury, and at least one of the following items: abnormal wall motion, regional wall thinning, or dilatation of the LV; perfusion defect on thallium-201 myocardial scintigraphy or abnormal accumulation by gallium-67-citrate scintigraphy or technetium-99m-pyrophosphatemyocardial scintigraphy; abnormal intracardiac pressure, low cardiac output, or depressed LVEF; and interstitial fibrosis or cellular infiltration over moderate grade even if the findings were non-specific. All patients underwent coronary angiography, and no significant coronary artery stenosis was noted. All baseline characteristics, including CMR data, were collected within 1 month before steroid therapy initiation. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Study equation,[12] with coefficients modified for Japanese patients,[13] as follows: estimated glomerular filtration rate (mL/min/1.73 m^2) = 194×serum creatinine$^{-1.094}$ × age$^{-0.287}$×(0.739 if female).

As per the standard protocol,[14] CS patients administered a starting dose of 60 mg prednisolone on alternate days for 1 month, and this dose was tapered gradually to the final maintenance dose of 10 mg on alternate days. All study patients received the final maintenance dose of prednisolone after 6 months. No patients enrolled in this study were receiving immunosuppressant therapy. This study was approved by the ethics committee of National Cerebral and Cardiovascular Center, and patients gave informed consent.

Echocardiography

All patients underwent echocardiographic examinations with commercially available ultrasonography systems before and 6 months after initiation of steroid therapy. LV volumes and LVEF were measured by the modified Simpson's method, according to the guidelines of the American Society of Echocardiography.[15]

CMR imaging

CMR imaging was performed using a 1.5-T MR system (Magnetom Sonata, Siemens, Erlangen, Germany) with a standardised clinical protocol. All CMR images were electrocardiographically gated and obtained during repeated breath-holds. Cine images were acquired with a steady-state free precession (SSFP) with the following parameters: repetition time, 3.2 ms; echo time, 1.6 ms; flip angle, 55°; matrix, 190×190; field of view, 340 mm; section thickness, 6 mm; section interval, 10 mm; sensitivity encoding factor, 2. After localisation of the heart, cine images of 9–12 contiguous short-axis sections encompassing the entire LV and 2-, 3-, and 4-chamber long-axis sections were collected. Then, gadopentetate meglumine (0.15 mmol/kg; Magnevist; Schering AG, Berlin, Germany) was administered at a rate of 3–4 mL/s using a power injector. LGE images were acquired 10 min after the injection of gadopentetate meglumine, with an inversion-recovery SSFP pulse sequence with inversion time of 300 ms.[16 17] The parameters used in SSFP for LGE were repetition time, 3.5 ms; echo time, 1.7 ms; flip angle, 60°; matrix, 256×129; field of view, 340 mm; section thickness, 8 mm; section interval, 10 mm; sensitivity encoding factor, 1. Among the 9–12 short-axis slices, we excluded both ends of the apex and the base because the scans of these sections did not include the LV muscle or the bevelled myocardium, which caused incorrect signal intensities. Then, seven adjacent slices in the middle of the remaining slices were obtained by using localiser of LV long-axis.[17]

CMR data analyses

Cine images were analysed using ARGUS (Siemens, Germany) to calculate LV volumes, mass and function. LGE images were analysed using Ziostation 2 (Ziosoft, Tokyo, Japan). Regions of LGE in seven slices of short-axis LGE imaging were automatically defined as those exhibiting signal intensity above a predetermined threshold. We used a threshold of 5 SDs above the signal intensity of non-damaged myocardium, because LGE quantification with the threshold of 5SD demonstrated the best agreement with visual assessment and best reproducibility among different techniques with different thresholds, as previously reported.[18 19] The LGE mass was calculated using the LGE area obtained from the seven LGE imaging slices. The extent of LGE was expressed as a percentage of LV mass according to the following equation:

$$\text{LGE mass}\,(\%) = \{\text{LGE mass (g)}\}/\{\text{LV mass (g)}\} \times 100.$$

The patients were divided into two groups using the median value for the extent of LGE: small-extent LGE group (LGE <20%) and large-extent LGE group (LGE ≥20%). The methods used for assessing LGE and representative images for both groups are shown in figure 1.

Clinical follow-up

The primary composite outcome was defined as cardiac death, hospitalisation for heart failure, and life-threatening arrhythmia. Life-threatening arrhythmia was defined as documented or appropriate implantable cardioverter defibrillator treatment for termination of ventricular fibrillation or sustained ventricular tachycardia and successful cardiopulmonary resuscitation for cardiac arrest. Follow-up information was obtained by retrospective chart review. The composite end-point included only the first event for each patient. If a patient was admitted to our hospital due to heart failure and then died of heart failure, it counted as one event. Additionally, we did not count hospital admissions due to non-cardiac causes as events of hospital admission. No patients were lost to follow-up.

Statistical analyses

All data are expressed as means±SD. Statistical analyses were performed using JMP10 (SAS Institute, Cary, North Carolina, USA). A p value less than 0.05 was considered statistically significant. Continuous variables were compared using paired or unpaired Student t test, as appropriate. Categorical variables of the two groups were compared using the χ^2 test. Long-term survival was estimated by Kaplan–Meier analysis, and differences in survival were assessed using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were constructed to investigate the predictors of baseline data for combined adverse outcomes. Echocardiographic measurements were used for analysis of pretherapy and post-therapy LV volumes and LVEF. Pearson's correlation coefficient analysis was used to assess the correlation between extent of LGE and LVEF changes. Multivariate linear regression analysis was also performed with adjustment for LVEF. Receiver-operating characteristic (ROC) curve was used to examine the performance characteristic of %LGE mass. Area under the curve (AUC), and 95% confidence of ROC curve, were calculated to provide a measure of the accuracy of %LGE mass to predict combined adverse outcomes. Variables with a p value <0.05 in the univariate models were included in the multivariate analysis.

RESULTS

Overall, 71 patients were diagnosed with CS. Of these, 21 were excluded because they did not undergo CMR. Among the 50 CS patients who underwent CMR, seven patients, including two patients without LGE, were excluded because they did not receive steroid therapy. Eventually, 43 patients met the inclusion criteria for this study (15 men and 28 women; mean age, 59 ±10 years; age range, 29–73 years). The mean follow-up duration was 39±19 months (range, 8–73 months). Twenty-two patients were assigned to the large-extent LGE group, and 21 patients were assigned to the small-extent LGE group, using the median value for the extent of LGE.

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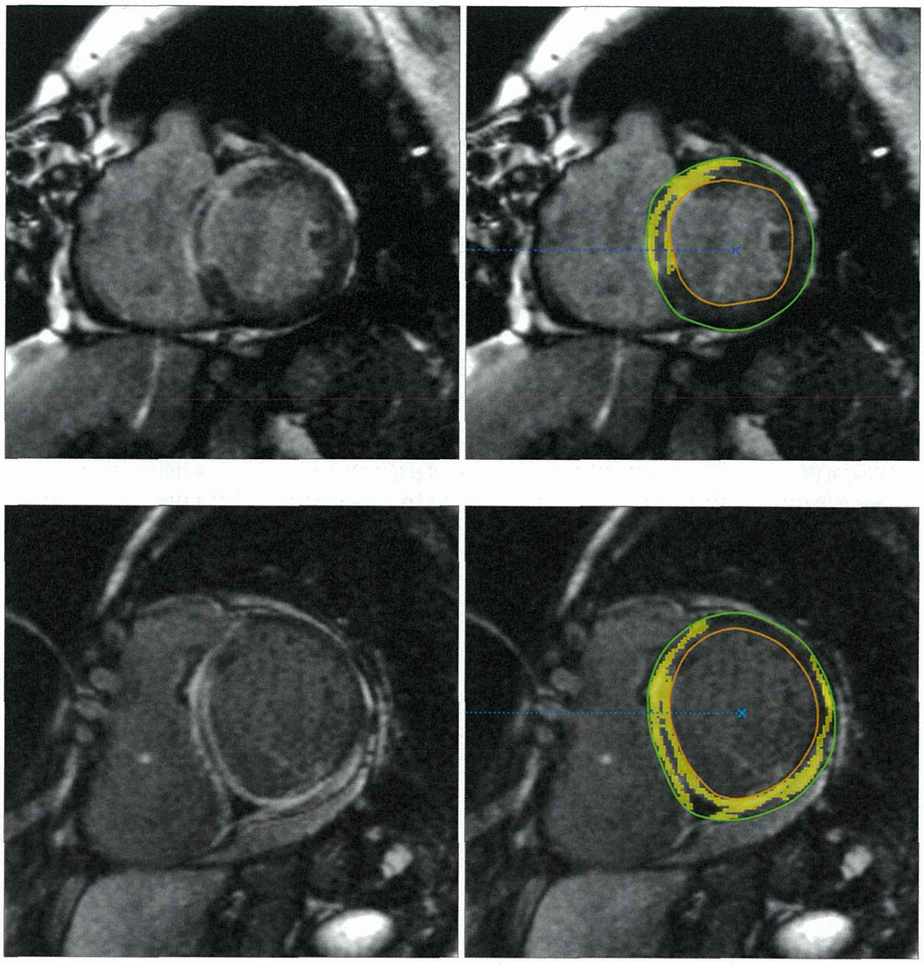

Figure 1 Quantification of the volume of late gadolinium enhancement (LGE) in CMR. (A, B) are representative images from patients with small-extent LGE and large-extent LGE, respectively. Left panels show original LGE images, and right panels indicate the automatically coloured LGE area according to the following predetermined setting: 5 SDs above the mean signal intensity of remote non-diseased myocardium.

Baseline characteristics

Patient baseline characteristics are summarised in table 1. Demographic factors, New York Heart Association (NYHA) functional class, and organ involvement did not differ between the two groups. The B-type natriuretic peptide (BNP) level in the small-extent LGE group was significantly lower than that in the large-extent LGE group. No significant differences in systemic inflammatory markers, indicating the activity of systemic sarcoidosis, were observed between the two groups. Before initiation of steroid therapy, there was also no difference between the two groups in type of medication or implanted device, including permanent pacemaker, implantable cardioverter-defibrillator, and cardiac resynchronisation therapy.

Echocardiographic data and CMR analysis

Echocardiographic and CMR data before steroid therapy are also shown in table 1. CMR was performed 13±7 days before the initiation of steroid therapy. Lower LVEF and higher LV end-diastolic and end-systolic volume indices were observed in the large-extent LGE group before steroid therapy. Although the difference between the two groups was not statistically significant, there was a trend toward larger LV mass in the large-extent LGE group.

Extent of LGE as a predictor of adverse events

During the follow-up period, six patients died of heart disorders, including five patients with heart failure and one patient with refractory ventricular arrhythmia. There were no non-cardiac deaths in this study. Additionally, 11 patients were hospitalised for heart failure, and six suffered life-threatening arrhythmia. Among these six life-threatening arrhythmias, five patients suffered sustained ventricular tachycardia, and one patient suffered ventricular fibrillation. Four of the five ventricular tachycardia cases were identified by the implantable cardioverter defibrillator electrogram; three cases were terminated by appropriate shock, and one case by antitachycardia pacing. Furthermore, one ventricular tachycardia case, with symptoms of palpitation and decreased blood pressure, was identified by ECG and terminated by cardioversion. Implantable cardioverter defibrillator was implanted in him after the event.

There were no cardiac deaths in the small-extent LGE group during the follow-up period. The survival rate in the large-extent LGE group was lower than that in the small-extent LGE group: 95% after 1 year, 77% after 3 years, and 72% after 5 years. A log-rank test revealed a significant difference in combined adverse outcomes (log-rank: $\chi^2=8.10$, p=0.004), cardiac mortality (log-rank: $\chi^2=6.36$, p=0.012), and hospitalisation for heart failure (log-rank: $\chi^2=8.60$, p=0.003) (figure 2) between the small-extent and large-extent LGE groups. On the other hand, extent of LGE did not appear to be associated with future occurrences of life-threatening arrhythmias (log-rank: $\chi^2=0.87$, p=0.352). The univariate Cox proportional hazards model showed that the extent of LGE expressed as %LGE mass, NYHA functional class, BNP and LVEF were associated with