Longitudinal Change in Renal Function in Patients With Idiopathic Dilated Cardiomyopathy Without Renal Insufficiency at Initial Diagnosis

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Background Impaired renal function is associated with poor outcomes among patients with chronic heart failure (CHF). However, the long-term changes in renal function in CHF patients without renal insufficiency at initial diagnosis remain unclear.

Methods and Results Retrospective analysis of patients presenting with idiopathic dilated cardiomyopathy (IDCM) from 1984 to 2003 and who had normal renal function defined as estimated creatinine clearance (eCcr) ≥ 60 ml/min at the first diagnosis. Cumulative event proportions and renal insufficiency defined as eCcr < 60 ml/min were calculated by the Kaplan-Meier method. The predictors of renal insufficiency were evaluated by logistic regression analysis. Impaired renal function developed in 20% during an 8-year follow-up and in 50% during a 20-year follow-up. Advanced age at the first diagnosis, high frequency of admissions, and hypotension during the clinical course were associated with the occurrence of impaired renal function. Beta-blocker therapy was a negative predictor of renal insufficiency.

Conclusions In patients with IDCM without renal insufficiency at initial diagnosis, worsening renal function occurred during the follow-up period. Frequent admissions, hypotension, and lacking β -blocker therapy were associated with a poor prognosis in renal function. (Circ J 2007; 71: 1927–1931)

Key Words: eCcr; Heart failure; Idiopathic dilated cardiomyopathy; Renal insufficiency

Heart failure (HF), including idiopathic dilated cardiomyopathy (IDCM), had a poor prognosis in the past^{1–3} but the beneficial effects of angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB) and β -blockers have improved the survival of patients with HF.^{4–9} However, because patients with HF are surviving longer, the incidence of renal dysfunction has increased, which can make therapy more difficult.^{10,11} “Cardiorenal syndrome” indicates the presence or development of renal dysfunction in patients with HF, and has a bad prognosis.^{10,12} Recent studies have revealed that renal function, as measured by estimated glomerular filtration rate (GFR), is strongly associated with mortality in patients with HF.^{13,14} Furthermore, once patients are admitted to hospital, worsening renal function implies a worse prognosis.^{15–17} Thus, therapy offering renal protection seems to be important in patients with HF.

So far, consensus as to the management of cardiorenal syndrome has not been achieved. Revealing the longitudinal

change in renal function and its predictors in patients with HF is crucial to establishing better therapy for both HF and cardiorenal syndrome.¹¹ However, to our knowledge, there are few reports on the risk for impaired renal function and few reports of long-term follow-up to examine if renal dysfunction has increased in patients with HF. Therefore, the purpose of this study was to reveal the long-term changes in renal function in patients with IDCM without renal insufficiency at initial diagnosis. Furthermore, we examined various clinical parameters as the predictive values of the clinical course of renal function.

Methods

Patient Population

We performed a retrospective analysis of patients with IDCM who were referred to Niigata University Medical and Dental Hospital between 1983 and 2003. The diagnosis of IDCM was based on careful medical history, physical examination, chest radiography, electrocardiography, blood test, echocardiography, and cardiac catheterization. All patients underwent cardiac catheterization after improvement of HF symptoms. All patients were free of ischemic heart disease, valvular heart disease, congenital heart disease, and other cardiomyopathies. Patients who had renal insufficiency at the first diagnosis were excluded. Renal insufficiency was defined as estimated creatinine clearance (eCcr) < 60 ml/min, calculated by using the Cockcroft-Gault equation: $[(140 - \text{age}) \times \text{body weight (kg)}] / [72 \times \text{serum creatinine (mg/dl)}]$, multiplied by 0.85 for women.^{12,13}

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Table 1 Baseline Clinical Characteristics of 70 Patients With IDCM

<i>Clinical characteristics</i>	
Age (years)	48.0±1.6
Sex (F/M)	17/53
DM	8 (11.4%)
HT	12 (17.1%)
AF	17 (24.3%)
U-protein	6 (8.6%)
Hematuria	1 (1.4%)
eCcr (ml/min)	94.57±4.69
<i>Hemodynamic characteristics</i>	
SBP (mmHg)	118.3±2.0
DBP (mmHg)	73.1±1.5
LVEF (%)	35.84±1.15
CI (L·min ⁻¹ ·m ⁻²)	2.90±0.10
LVEDVI (ml/m ²)	123.0±4.2

Data are mean±standard error of mean for continuous variables and numbers (proportions) for categorical variables.

IDCM, idiopathic dilated cardiomyopathy; DM, diabetes mellitus; HT, hypertension; AF, atrial fibrillation; U-protein, urinary protein; eCcr, estimated creatinine clearance; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; CI, cardiac index; LVEDVI, left ventricular end diastolic volume index.

Follow-up

IDCM patients underwent periodic medical checkups and received the standard therapy, ACEI, ARB, and β -blockers, by the hospital's cardiologists. The decision to use each drug in individual cases was left to the attending physician. The endpoint of follow-up was the occurrence of renal insufficiency defined as eCcr <60 ml/min. The non-survivors were considered as censored cases at that point in time. Data including frequency of admission for HF, left ventricular ejection fraction (LVEF), and diastolic left ventricular diameter were recorded just before the occurrence of renal insufficiency as follow-up data. The ratio of LVEF improvement (Δ LVEF) was calculated as: $100 \times [(LVEF \text{ just before the end point of follow-up}) - (LVEF \text{ at initial diagnosis})] / (LVEF \text{ at initial diagnosis})$. The existence of hypotension was defined as systolic blood pressure (BP) <80 mmHg persisting for at least 6 months before the occurrence of renal insufficiency.

Statistical Analysis

Patients' characteristics were expressed as mean±standard error of mean for continuous variables and as numbers

Fig 1. Kaplan-Meier survival curve for the cumulative proportion without the occurrence of renal insufficiency.

(proportions) for categorical variables. Cumulative event proportion was evaluated by Kaplan-Meier survival analysis. Potential risk factors for the occurrence of renal insufficiency were evaluated by Cox proportional hazards regression for the baseline data at initial diagnosis, and by logistic regression for the data observed during follow-up. An age-adjusted model and additional forward selection method were used for both the Cox and logistic regression analyses. All analyses were performed using SPSS version 12.0J (Chicago, IL, USA). Two-sided statistical significance was taken as $p < 0.05$.

Results

Baseline Patients' Characteristics

The baseline clinical characteristics of 70 patients with IDCM are summarized in Table 1 (17 women, 53 men; mean age 48.0±1.6 years). Eight (11.4%) patients also had diabetes mellitus (DM), 12 (17.1%) had hypertension, and 17 (24.3%) had atrial fibrillation. Mean LVEF measured by cardiac catheterization was 35.84±1.15% and the mean cardiac index (CI) was 2.90±0.10 L·min⁻¹·m⁻². The mean eCcr was 94.57±4.69 ml/min and >60 ml/min in all patients.

Longitudinal Change in Renal Function in Patients With IDCM

The Kaplan-Meier survival curve showed the time and

Table 2 Potential Risk Factors at the Initial Diagnosis for the Occurrence of Renal Insufficiency

	Hazard ratio*	p value	Hazard ratio**	p value
Age	1.115 (1.059–1.174)	<0.001	1.112 (1.050–1.178)	<0.001
Sex (F/M)	0.625 (0.208–1.875)	0.401		0.304
DM (yes/no)	0.403 (0.090–1.796)	0.233		0.266
HT (yes/no)	1.244 (0.363–4.266)	0.729		0.505
AF (yes/no)	0.744 (0.240–2.304)	0.608		0.815
U-protein (yes/no)	3.915 (0.980–15.64)	0.054		0.079
Hematuria (yes/no)	0.000 (0.000–0.000)	0.985		0.646
eCcr	1.010 (0.983–1.038)	0.465		0.718
SBP	0.993 (0.965–1.022)	0.626		0.582
DBP	1.022 (0.986–1.059)	0.234		0.568
LVEF	1.024 (0.970–1.081)	0.393		0.491
CI	0.641 (0.350–1.174)	0.149		0.390
LVEDVI	1.012 (0.996–1.029)	0.151		0.295

Hazard ratio (95% confidence interval), per 1-unit increment unless otherwise noted.

*Age-adjusted hazard ratio; non-adjusted for age and age-adjusted for all other variables. **Hazard ratio by forward selection method; noted only for selected variables in the final equation. Age is always adjusted in every step.

Abbreviations see in Table 1.

Table 3 Clinical Characteristics of 70 Patients With IDCM During Follow-up

Frequency of admission for HF	1.84±0.24
ΔLVEF (%)	20.5±7.00
New-onset DM	22 (31.4%)
New-onset AF	9 (12.9%)
ACEI therapy	49 (70.0%)
ARB therapy	17 (24.3%)
-blocker therapy	58 (82.9%)
LVEDd (cm)	6.07±0.12
Hypotension	4 (5.7%)

HF, heart failure; ΔLVEF, $100 \times [(LVEF \text{ just before the end point of follow-up}) - (LVEF \text{ at the initial diagnosis})] / (LVEF \text{ at the initial diagnosis})$; LVEDd, left ventricular end diastolic diameter; Hypotension, SBP < 90 mmHg persisting for at least 6 months before the occurrence of renal insufficiency. Other abbreviations see in Table 1.

cumulative proportion without the occurrence of renal insufficiency. The calculated cumulative proportion of event-free promotion at 8 and 20 years follow-up was 80.2% and 50.2%, respectively (Fig 1).

Potential Risk Factors at Initial Diagnosis for the Occurrence of Renal Insufficiency

Potential risk factors at the initial diagnosis for the occurrence of renal insufficiency are summarized in Table 2. Age at the initial diagnosis (hazard ratio 1.112, $p < 0.001$) was the factor most strongly associated with the occurrence of renal insufficiency. The presence of urinary protein at the initial diagnosis ($p = 0.079$) meant that impaired renal function was likely to occur. No other risk factors were identified in this analysis as risk factors at the initial diagnosis.

Predictors for the Occurrence of Renal Insufficiency During Follow-up

The characteristics of the 70 patients with IDCM during the follow-up period are summarized in Table 3. Fifty-eight (82.9%) tolerated long-term oral -blocker therapy; 41 (58.6%) were treated with metoprolol, 10 (14.2%) were treated with carvedilol, 4 (5.7%) were treated with atenolol, and other -blockers were used in 4 patients (5.7%). Mean maintenance doses were 54.1 ± 4.5 mg for metoprolol, 9.6 ± 1.7 mg for carvedilol, and 18.8 ± 3.6 mg for atenolol. Reasons for not using -blocker therapy were bradyarrhythmia (4.3%), bronchial asthma (2.8%), hypotension (1.4%), and unknown (8.6%). Predictors for the occurrence of renal

Fig 2. Kaplan-Meier survival curves for the cumulative proportion without the occurrence of renal insufficiency of Group ΔLVEF ≥20% and Group ΔLVEF <20%.

insufficiency during follow-up are summarized in Table 4. The occurrence of renal insufficiency was significantly higher in patients with high frequency of admission for the exacerbation of HF (odds ratio 1.750, $p = 0.004$) and patients with continuous hypotension (odds ratio 353.7, $p = 0.006$). Beta-blocker therapy was the predictor for preventing the occurrence of renal insufficiency (odds ratio 0.102, $p = 0.012$). The ratio of patients receiving ACEI and/or ARB was 87.1%, and these were not associated with elevated risk of renal insufficiency in this study.

Longitudinal Change in Renal Function Because of the Ratio of LVEF Improvement

The result of age-adjusted logistic regression analysis suggested ΔLVEF had a tendency to be a negative predictor (odds ratio 0.980, $p = 0.010$) for the occurrence of renal insufficiency. Fig 2 shows the differences in the Kaplan-Meier survival curve between Group ΔLVEF ≥20% and Group ΔLVEF <20%. There was a significant decrease in the occurrence of renal insufficiency in Group ΔLVEF ≥20% compared with Group ΔLVEF <20% (log-rank, $p = 0.011$). The respective calculated cumulative proportion without the occurrence of renal insufficiency at 8 and 20 years follow-up was 96.7% and 72.7% in ΔLVEF ≥20%, and 72.1% and 30.2% in Group ΔLVEF <20%.

Discussion

The importance of this study is that it reveals the longitu-

Table 4 Potential Risk Factors at the Initial Diagnosis for the Occurrence of Renal Insufficiency

	Odds ratio*	p value	Odds ratio**	p value
Frequency of admission for HF	1.456 (1.064–1.991)	0.019	1.750 (1.192–2.569)	0.004
ΔLVEF	0.980 (0.965–0.995)	0.010		0.134
New-onset DM (yes/no)	4.133 (1.217–14.04)	0.023		0.533
New-onset AF (yes/no)	3.824 (0.755–19.38)	0.105		0.379
ACEI therapy (yes/no)	0.680 (0.205–2.256)	0.529		0.726
ARB therapy (yes/no)	1.558 (0.425–5.711)	0.503		0.802
-blocker therapy (yes/no)	0.304 (0.077–1.203)	0.090	0.102 (0.017–0.603)	0.012
LVEDd	2.617 (1.321–5.182)	0.006		0.226
Hypotension (yes/no)	59.22 (2.478–1,415)	0.012	353.7 (5.195–24,084)	0.006

Odds ratio (95% confidence interval), per 1-unit increment otherwise noted.

*Age-adjusted odds ratio; non-adjusted for age and age-adjusted for all other variables. **Odds ratio by forward selection method; noted only for selected variables in the final equation. Age is always adjusted in every step.

Abbreviations see in Tables 1, 3.

dinal change of renal function in patients with IDCM without renal insufficiency at initial diagnosis; renal insufficiency, as defined by $\text{eCcr} < 60 \text{ ml/min}$, occurred in 20% during the first 8 years of follow-up and in 50% at the 20-year follow-up. In addition, we demonstrated that high frequency of admission for the exacerbation of HF, hypotension during the follow-up period, and not taking β -blocker therapy are prognostic factors for the worsening of renal function in these patients.

There are strong interactions between cardiovascular and renal disease. Renal dysfunction is an independent risk factor for the development of cardiovascular disease.^{12,19–21} Decreased GFR has consistently been found to be an independent risk factor for cardiovascular disease outcomes and all-cause mortality in patients with HF.^{13,14} Our data also indicated that 27% of patients who showed $\text{eGFR} < 60 \text{ ml/min}$ died from cardiovascular disease, compared with 6% of patients who showed $\text{eGFR} > 60 \text{ ml/min}$, during follow-up (data not shown). Because the risk of cardiovascular events becomes evident at an estimated GFR $< 60 \text{ ml/min}$, in the present study we defined $\text{cCcr} < 60 \text{ ml/min}$ as renal insufficiency.^{19,20,22,23} Our results suggest that in IDCM patients without renal insufficiency at their initial diagnosis, renal insufficiency occurs in 20% of during the first 8 years of follow-up and, surprisingly, in 50% at 20-year follow-up. DM is estimated to increase the risk of end-stage renal disease approximately 12-fold.²⁴ Although the proportion of the progression of renal disease in patients with DM is diverse, in general, renal function shows stable or hyper filtration for 10–15 years after diagnosis, and progression to renal insufficiency occurs after a follow-up of 20 years.^{24,25} Thus, our data suggests that the clinical course of renal function in patients with IDCM is likely to be worse.

Age at initial diagnosis was the factor most strongly associated with the occurrence of renal dysfunction. After stratification for age, high frequency of admission for the exacerbation of HF, hypotension, and β -blocker therapy remain associated with a change of renal function. Several reports have demonstrated that worsening renal function occurs frequently among hospitalized HF patients and is associated with worse outcomes.^{15–17} Forman et al speculated that renal deterioration was associated with inherent mechanisms of disease or to the impact of therapy administered on admission, because the worsening of renal function occurs early after admission. Our findings are consistent with, and could extend their findings; once patients were admitted, renal function worsened and did not recover completely to the level before admission, even after deteriorating HF was improved. In other words, renal function worsens not only sequentially but also step-by-step in accordance with admission because of deterioration of HF. Although the precise reasons are unknown from this study, there are some explanations. The use of diuretics for patients with HF is still controversial in terms of renal protection and is potentially less likely to improve renal function. We tried to evaluate the relationship between the use of diuretics and renal function, but because of fluctuations of the doses and use in some patients, correcting the data throughout the follow-up period was difficult to do retrospectively. Further study is needed to clarify this point. Another explanation for worsening renal function is the deterioration of HF itself. The renin–angiotensin system and sympathetic nerve activity became excessively stimulated during episodes of acute decompensation and both cause impaired renal function.²⁶ Neither ACEI nor ARB showed a significant relationship

with renal function in our study. The beneficial effects of both agents on renal function are well known from large clinical trials.^{27,28} In this study, 87.1% of the patients were treated with ACEI and/or ARB and this high proportion of the patients might have affected the analysis.

Braam et al suggest that the cardiorenal connection is an interactive network with positive feedback loops, including not only extracellular fluid volume and BP, but also the renin–angiotensin system, the balance between nitric oxide and reactive oxygen species, inflammation, and the sympathetic nervous system.¹² The mechanisms of HF-induced/associated impaired renal function are diverse and not well-defined.² Hemodynamic abnormalities, such as hypotension or low cardiac output, and neurohumoral factors, including endothelin, nitric oxide, prostaglandin and natriuretic peptides, are thought to play an important role.¹⁰ Our results also imply that hypotension has an important role in the progression of renal dysfunction. The CI at initial diagnosis was not associated with changes in renal function. Lungman et al demonstrated that renal blood flow could be preserved if the CI remained above $1.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{mm}^{-1}$.²⁹ The mean CI at initial diagnosis in this study was $\text{L} \cdot \text{min}^{-1} \cdot \text{mm}^{-1}$, and renal blood flow may have been preserved. However, because there are no data on cardiac catheterization during the follow-up period, we could not determine the relationship between subsequent CI and renal function. However, in our study there was a significant difference in the progression of renal insufficiency between patients whose ΔLVEF improved more than 20% and those whose ΔLVEF improved less than 20%. β -blocker therapy, which has resulted in improved survival, morbidity, ejection fraction, and rate of hospitalization,³⁰ is also associated with beneficial results on renal function. These facts suggest that improvement of hemodynamic abnormalities has favorable effects on renal function in patients with HF via modulation of several factors.

Study Limitations

First, this was not a randomized, prospective study. Second, the number of subjects was small, and this might have affected the statistical analyses. Larger trials must be conducted to confirm our results.

Clinical Implications

The most important is that the clinical course of renal function in patients with IDCM is less likely to be good, even if renal function is preserved at initial diagnosis. We also must recognize that admission, hypotension, and not taking β -blocker therapy are associated with poor prognosis in renal function. We need to take meticulous care of HF patients and to choose therapies that offer renal protection for them. A prospective study is also needed to establish the best therapy for long-term management.

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