Objective

The relationship between mild-to-moderate renal dysfunction and cardiac diastolic dysfunction and cardiac events in patients with nonischemic dilated cardiomyopathy (NDCM) has not been fully elucidated. The aim of this study was to investigate the relationship between renal and cardiac function, as well as clinical outcome in patients with NDCM.

Methods

We measured plasma BNP and eGFR, and performed cardiac catheterization in 135 patients with NDCM. LV $dP/dt_{max}$ and $T_{1/2}$ were determined as indexes of LV contractility and isovolumic relaxation, respectively. During a mean follow-up of 4.8 years, we monitored all patients for the occurrence of cardiac events, which were defined as cardiac death (from worsening HF or sudden death) and unscheduled admission for decompensated HF.

Patients were classified into 3 groups on the basis of eGFR (mL min$^{-1}$ 1.73 m$^{-2}$): eGFR ≥ 90 ($n = 23$, group A), 60 ≤ eGFR < 90 ($n = 70$, group B), and 30 ≤ eGFR < 60 ($n = 42$, group C). Whereas LV $dP/dt_{max}$ did not significantly differ among the 3 groups, $T_{1/2}$ was significantly longer in groups B and C than in group A ($P < 0.01$). Event-free survival in group C was significantly lower than that in groups A and B ($P = 0.014$, log-rank test).

These results suggest that even mild renal dysfunction is associated with LV isovolumic relaxation impairment. In addition, moderate impairment of renal function is independently associated with cardiac events in patients with NDCM.


Key words: Dilated cardiomyopathy, Relaxation, Renal dysfunction, Prognosis

Chronic heart failure (HF) is associated with a high mortality rate and requires repeated and prolonged hospitalization. Chronic kidney disease (CKD) is also a serious public health problem. The prevalence of renal dysfunction in individuals with chronic HF has been reported to be approximately 25%.1) CKD contributes to reduced cardiac function, cardiac hypertrophy, and an increased risk of adverse cardiovascular events. Such interactions between CKD and HF represent the pathophysiological basis for the clinical entity known as cardiorenal syndrome.2) Renal dysfunction is an independent predictor of prognosis in patients with HF.3-7) However, most previous studies examining this issue have included patients with ischemic heart disease or a preserved ejection fraction (EF). Therefore, the relationship between renal and myocardial dysfunction in patients with nonischemic dilated cardiomyopathy (NDCM), especially those with mild renal dysfunction, remains unknown. In addition, given that cardiac function was assessed indirectly by echocardiography in the previous studies,8,9) little is known about the effect of renal dysfunction on left ventricular (LV) function as measured directly with a pigtail catheter equipped with a high-fidelity micromanometer, which provides a relatively load-insensitive evaluation of contractile performance.9,10) Here, we used cardiac catheterization with a micromanometer to investigate the relationship between CKD and cardiac function, as well as the association between CKD and clinical outcome in patients with NDCM and mild-to-moderate impairment of renal function.

Methods

Study population: We studied 135 consecutive patients with NDCM (mean age, 52 years; range, 20 to 78 years) who were referred to Nagoya University Hospital between March 2000 and August 2008. All patients were Japanese. The 76 patients who had previously been hospitalized for acute heart failure were receiving treatment and were in stable condition before their referral to Nagoya University Hospital for cardiac catheterization. The remaining patients were asymptomatic and were identified on the basis of an electrocardiogram abnormality at an annual health check. NDCM was defined on the basis of the presence of both a reduced LV ejection fraction (LVEF) (< 50% as determined by contrast left ventriculography) and a dilated LV cavity in the absence of coronary or valvular heart disease.
disease, hypertension, or cardiac muscle disease caused by any known systemic condition. Prior acute coronary syndrome or myocardial infarction was excluded. A baseline for estimated glomerular filtration rate (eGFR) was calculated with the use of a revised equation for Japanese individuals, which incorporates age, sex, and serum creatinine concentration.\textsuperscript{13} eGFR (mL min\(^{-1}\) 1.73 m\(^3\)) for males was calculated as 194 × (serum creatinine)\(^{-1.094}\) × (age)\(^{-0.287}\), whereas that for females was calculated with the same equation with the result multiplied by a correction factor of 0.739. Patients were classified into 3 groups on the basis of eGFR (mL min\(^{-1}\) 1.73 m\(^3\)): group A, eGFR ≥ 90; group B, 60 ≤ eGFR < 90; and group C, 30 ≤ eGFR < 60. Group A was defined as CKD stage 1 with a normal GFR, group B as CKD stage 2 with mild impairment of GFR, and group C as CKD stage 3 with moderate impairment of GFR, according to the guidelines for CKD.\textsuperscript{14} Patients with a baseline eGFR of < 30 mL min\(^{-1}\) 1.73 m\(^3\) were excluded from the study. Diabetes mellitus (DM) was diagnosed on the basis of fasting plasma glucose concentration of ≥126 mg/dL.\textsuperscript{15} The study protocol complied with the Declaration of Helsinki and was approved by the appropriate institutional review committee. Written informed consent was obtained from all patients.

Biochemical data: Blood samples were collected from the antecubital vein of fasted patients after they had rested for 20 minutes in the supine position. All patients were in clinically stable condition. Routine blood biochemical analysis was performed in addition to measurement of the plasma levels of brain natriuretic peptide (BNP), renin activity, aldosterone, and epinephrine as described previously.\textsuperscript{16}

Echocardiography: We performed M-mode, two-dimensional, and pulsed Doppler echocardiography with a phased-array electronic ultrasound system (Vivid 7, GE Healthcare, Milwaukee, WI, USA), and measured septal and LV posterior wall thickness as well as LV end-diastolic and end-systolic dimensions. Echocardiographic LV mass was calculated by the area-length method as recommended by the American Society of Echocardiography.\textsuperscript{17} The LV mass index was calculated by dividing the LV mass by body surface area. The peak flow velocities at the mitral level during rapid filling (E) and during atrial contraction (A), the E/A ratio, and the deceleration time were calculated from the pulsed Doppler echocardiographic data. The tissue Doppler imaging wave of the mitral annulus was obtained from the septal side of the apical 4-chamber view. Analysis was performed for the early diastolic filling velocity (E′). The ratio of early transmural flow velocity to early diastolic mitral annular velocity (E/E′) was taken as an estimate of LV filling pressure. Two examiners who were unaware of the clinical status of the subjects performed the echocardiographic analysis.

Cardiac catheterization: Cardiac catheterization was performed by experienced technologists. Pulmonary artery wedge pressure (PAWP) and cardiac output were measured with the use of a Swan-Ganz catheter as previously described.\textsuperscript{18} A fluid-filled 6F pigtail catheter equipped with a high-fidelity micromanometer (model SPC-464D; Millar Instruments, Houston, TX, USA) was advanced into the left ventricle through the right radial artery for measurement of LV pressure. Micromanometer pressure signals and standard electrocardiograms were recorded with a multichannel recorder (MR-40; TEAC, Tokyo) throughout the procedure. LV pressure signals were digitized at 3-ms intervals and analyzed with a 32-bit microcomputer system and software developed in-house. Steady-state LV pressure data were selected for analysis. We calculated the maximal first derivative of LV pressure (LV dP/dt\(_{max}\)) as an index of contractility. To evaluate LV isovolumic relaxation time, we computed the pressure half-time (T\(_{1/2}\)) directly, as previously described.\textsuperscript{19} After completion of LV pressure measurements, selective coronary angiography as well as left ventriculography were performed. A right ventricular biopsy was also obtained to exclude myocarditis or specific heart muscle disease.

Follow-up: We followed up all patients for the occurrence of cardiac events, which were defined as cardiac death (from worsening HF or sudden death) and unscheduled admission for decompensated HF.

Statistical analysis: Data are expressed as the mean ± SD. Comparison of continuous variables among groups was performed by one-way analysis of variance followed by Scheffe’s test, or by the Kruskal-Wallis test, as appropriate. Categorical data were compared by chi-square analysis. The associations between T\(_{1/2}\) and potential confounders were assessed with a multivariate linear regression model. We used a Cox proportional hazards model to estimate hazard ratios with a 95% confidence interval (CI), with multivariate adjustment for age, sex, and DM. Cumulative survival estimates were calculated by the Kaplan-Meier method, with differences among the survival curves being assessed by the log-rank test. All statistical analysis was performed with SPSS 17.0 software (SPSS, Chicago, IL, USA). A P value of < 0.05 was considered statistically significant.

### Table I. Baseline Clinical Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n = 23)</th>
<th>Group B (n = 70)</th>
<th>Group C (n = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.5 ± 12</td>
<td>50.7 ± 12</td>
<td>58.1 ± 12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>16/7</td>
<td>58/12</td>
<td>29/13</td>
<td>0.19</td>
</tr>
<tr>
<td>DM (%)</td>
<td>18.1</td>
<td>8.7</td>
<td>35.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>11</td>
<td>11</td>
<td>14</td>
<td>0.78</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>23.8 ± 5.8</td>
<td>24.1 ± 4.6</td>
<td>22.9 ± 3.8</td>
<td>0.12</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>II/III/IV</td>
<td>11/12/60</td>
<td>48/18/40</td>
<td>16/20/40</td>
</tr>
<tr>
<td>β-Blockers (%)</td>
<td>39.1</td>
<td>42.9</td>
<td>47.6</td>
<td>0.79</td>
</tr>
<tr>
<td>ACEIs or ARBs (%)</td>
<td>60.9</td>
<td>75.7</td>
<td>81.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>60.9</td>
<td>61.4</td>
<td>81.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Spironolactones (%)</td>
<td>39.1</td>
<td>41.4</td>
<td>61.9</td>
<td>0.07</td>
</tr>
</tbody>
</table>

The probability of event-free survival in group C was significantly lower than that in groups A and B by the log-rank test (P = 0.014). Continuous variables are expressed as the mean ± SD. P values are from analysis of variance tests (for continuous variables) or chi-square tests (for categorical variables).
Cardiac catheterization data:

- Heart rate (beats/minute): 86.8 ± 11.1
- Cardiac index (L min⁻¹ m⁻²): 3.09 ± 0.52
- PAWP (mmHg): 11.9 ± 6.2
- Systolic PA pressure (mmHg): 26.6 ± 8.1
- Right atrial pressure (mmHg): 5.4 ± 3.4
- Systolic blood pressure (mmHg): 118.3 ± 20.5
- Diastolic blood pressure (mmHg): 77 ± 14.6
- LV end-diastolic pressure (mmHg): 12.2 ± 8.5
- LVEF (%): 40.1 ± 9.3
- LVEDVI (mL/m²): 100.5 ± 45.0
- LVESVI (mL/m²): 63.3 ± 39.0
- LV dP/dt max (mmHg/s): 1158 ± 361
- T₂/2 (ms): 143 ± 183

Data are the mean ± SD.  \( P < 0.05 \) versus group A.  \( P < 0.05 \) versus group B.  \( E' \) indicates early diastolic filling velocity;  \( E/E' \), ratio of early transmural flow velocity to early diastolic mitral annular velocity;  \( IVS \), interventricular septum;  \( PA \), pulmonary artery;  LVESVI, LV end-diastolic volume index; and  LVESVI, LV end-systolic volume index.

Also, we observed significantly greater in group C than in group A, with a low eGFR. Drug treatment at baseline included diuretics in 91 patients (67.4%), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs) in 101 patients (74.8%), and \( \beta \)-blockers in 58 patients (43.0%).

The relationship between hemodynamic parameters and renal function: There was a significant correlation between eGFR and \( T_{2/2} \), as an index of LV isovolumic relaxation (B).
and $T_{1/2}$ among the study subjects, whereas there was no such correlation between eGFR and $LV dP/dt_{max}$ (Figure 1). We performed univariate and multivariate regression analysis of $T_{1/2}$ with eGFR, the prevalence of DM, plasma BNP level, LV end-diastolic diameter, PAWP, and LVEF as explanatory variables (Table III). Multivariate linear regression analysis revealed that eGFR was independently correlated with $T_{1/2}$ ($P = 0.039$).

**Clinical outcome:** The cumulative probability of event-free survival was calculated by the Kaplan-Meier method (Figure 2). During a mean follow-up of 4.8 years (range, 0.3 to 9.1 years), there were 40 cardiac events that included 10 cardiac deaths and 30 admissions due to worsening HF. Whereas no individuals in group A experienced cardiac death, 5 subjects in each of groups B and C died due to a cardiac event. Four individuals in group A and 13 subjects in each of groups B and C were hospitalized for worsening HF. The probability of event-free survival in group C was significantly lower than that in groups A or B by the log-rank test ($P = 0.014$).

To further assess whether renal dysfunction contributed to cardiac events, we applied a multivariable Cox proportional hazards model (Table IV). After adjustment for age, sex, and DM, the risk for cardiac events in group C tended to be higher than in group A (hazard ratio, 2.99; 95% CI, 0.87 to 10.19; $P = 0.079$). The risk of a cardiac event in group C after adjustment for age, sex, and DM was significantly higher than that in groups A and B combined (hazard ratio, 2.77; 95% CI, 1.21 to 6.34; $P = 0.016$).

### Table IV. Hazard Ratios (HRs) for Cardiac Events Stratified by eGFR Group

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Group B versus Group A</th>
<th>Group C versus Group A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariable</td>
<td>HR: 0.93, 95% CI: 0.31 - 2.84, p = 0.93</td>
<td>HR: 2.75, 95% CI: 0.92 - 8.20, p = 0.069</td>
</tr>
<tr>
<td>Multivariable adjusted for age and sex</td>
<td>HR: 1.16, 95% CI: 0.37 - 3.60, p = 0.80</td>
<td>HR: 3.91, 95% CI: 1.20 - 12.66, p = 0.023</td>
</tr>
<tr>
<td>Multivariable adjusted for age, sex, and DM</td>
<td>HR: 1.11, 95% CI: 0.34 - 3.50, p = 0.86</td>
<td>HR: 2.99, 95% CI: 0.87 - 10.19, p = 0.079</td>
</tr>
<tr>
<td>Group C versus Groups A + B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariable</td>
<td>HR: 3.61, 95% CI: 1.67 - 7.81, p = 0.0022</td>
<td></td>
</tr>
<tr>
<td>Multivariable adjusted for age and sex</td>
<td>HR: 3.48, 95% CI: 1.64 - 7.39, p = 0.0011</td>
<td></td>
</tr>
<tr>
<td>Multivariable adjusted for age, sex, and DM</td>
<td>HR: 2.77, 95% CI: 1.21 - 6.34, p = 0.016</td>
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</tbody>
</table>

**DISCUSSION**

We observed that renal insufficiency, even when mild, was associated with cardiac diastolic dysfunction in patients with NDCM. Our major finding was that moderate renal dysfunction was an independent risk factor for cardiac hospitalization and cardiac death in ambulatory patients with NDCM. The association between renal insufficiency and these two cardiac events was independent of diabetes, sex, and age, which are known risk factors for cardiovascular events. There appeared to be no increased risk of cardiac events among patients with mild renal insufficiency ($60 \leq eGFR$ (mL min$^{-1}$ 1.73 m$^{-2}$) $< 90$). These results might indicate the importance of renal insufficiency as a prevalent and potent risk factor for cardiac outcome among NDCM patients, even among those with moderate systolic dysfunction and relaxation impairment, and they suggest that it is beneficial to control this risk factor by appropriate medical therapy at the earliest possible stage.

In the early stages of HF, GFR is well maintained by compensatory increases in the filtration fraction, but in patients with more severe chronic HF, GFR becomes more dependent on afferent arteriolar blood flow and the stimulation of hemodynamic and hormonal pathways. Furthermore, the fall in effective renal blood flow is disproportionately more pronounced than the reduction in cardiac output. Nevertheless, it has been demonstrated that renal hemodynamic reserve is already impaired in patients with asymptomatic left ventricular dysfunction. Traditionally, the contribution of the kidneys to chronic HF has been considered an adaptive response mechanism, in which a series of compensatory neurohormonal changes, in particular, increased adrenergic drive and activation of the renin-angiotensin-aldosterone system (RAAS), are evoked to maintain the perfusion of vital organs and to expand the inadequate arterial blood volume. With respect to the kidneys, however, activation of the RAAS is not only a response to preserve systemic circulatory volume; rather, it is primarily a response to preserve GFR as renal blood flow decreases and renal perfusion pressure declines. Therefore, it can be postulated that the association between renal function and cardiac events is associated with neurohormonal activation. This notion is further supported by studies that show that renal function correlates with neurohormonal activation, including activation of the RAAS and adrenergic system, and that inhibition of this activation improves the renal dysfunction response to injury in patients and animals with chronic HF. It should be noted that in our cohort of patients with NDCM, there were no significant differences in plasma levels of epinephrine, renin activity, and aldosterone among the 3 experimental groups. This discrepancy in the level of neurohormonal activation observed in our study and previous studies may be due to differences in patients with severe or mild-to-moderate renal dysfunction and/or cardiac dysfunction. Further investigations into these issues are required.

Diastolic function assessed by echocardiography was previously found to be impaired in patients with advanced renal failure. $E/E'$ has been widely adopted as a noninvasive estimate of intracardiac filling pressure. However, this ratio may not be as reliable an indicator of intracardiac filling pressure in HF patients with advanced systolic dysfunction. In general,
cardiovascular diseases. Studies have included a high proportion of patients with ischemic cardiomyopathy in individuals with depressed systolic function, and many studies have previously been observed predominantly in patients with NDCM. Further studies are needed to determine the nature of the relationship between renal insufficiency and HF, and additional investigations should focus on whether stabilization of renal function and cardiac structure, function, and prognosis after myocardial infarction: the VALIANT Echo Study. J Am Coll Cardiol 2005; 50: 1238-45.

Our observations here demonstrate that moderate renal dysfunction enhances the risk of cardiac events in patients with NDCM. Further studies are needed to determine the nature of the relationship between renal insufficiency and HF, and additional investigations should focus on whether stabilization of renal insufficiency leads to improve cardiac diastolic dysfunction and cardiac outcomes.

An increased risk of mortality in persons with severe renal insufficiency has previously been observed predominantly in individuals with depressed systolic function, and many studies have included a high proportion of patients with ischemic cardiovascular diseases. Several mechanisms have been proposed to explain this increased mortality risk, including the possibilities that renal insufficiency has a higher prevalence in old people, and that it is associated with a higher burden of co-morbid illness such as diabetes. However, here we adjusted for diabetes and other risk factors such as age and sex and still observed an independent relationship between moderate renal insufficiency and cardiac events in ambulatory patients with NDCM. Renal function has been shown to be more closely associated with mortality in patients with advanced chronic HF than with any other established factor, including NYHA class and LVEF. Our findings suggest that clinicians caring for NDCM patients with mild to moderate HF must pay particular attention to even early stage renal insufficiency, as this is a common risk factor that carries important prognostic significance.

Study limitations: There are several limitations to the present study. First, it included a relatively small number of patients and a small number of events. Second, although medication was in general similar, not all patients were using the same drugs or doses of drugs. We did not investigate whether medications administered for CKD influence outcome in NDCM patients with renal dysfunction. Whether our findings will also hold for patients with more severe HF also requires further investigation.

In conclusion, the mild renal insufficiency was associated with cardiac diastolic dysfunction among these patients. However, there appeared to be no increased risk of cardiac events in patients with NDCM. Meanwhile, moderate renal insufficiency was an independent risk factor for cardiac events in patients with NDCM, even with mild to moderate symptoms. These results suggest that it is beneficial to control renal function by appropriate medical therapy at the earliest possible stage.

References


