Relationship Between Renal Function, Aortic Stiffness and Left Ventricular Function in Patients With Coronary Artery Disease

Hidekatsu Fukuta, MD; Nobuyuki Ohte, MD; Seiji Mukai, MD; Kaoru Asada, MD; Kazuaki Wakami, MD; Toshihiko Goto, MD; Genjiro Kimura, MD

Background: There are plausible reasons to hypothesize that increased aortic stiffness and left ventricular (LV) dysfunction may occur in early renal insufficiency.

Methods and Results: The correlation of glomerular filtration rate (GFR) with the augmentation index (AI) of ascending aortic pressure and indices of LV systolic and diastolic function (ejection fraction, LV pressure relaxation time constant, LV end-diastolic pressure and mitral inflow (E/A) and annular velocities (S’ and E’)) was examined in 359 consecutive patients undergoing cardiac catheterization for coronary artery disease (CAD). When patients were stratified according to GFR of 60, 75 and 90 ml·min⁻¹·1.73 m²⁻¹, there was a progressive increase in AI and decreases in E/A and E’ with decreasing GFR. There were no linear trends in other indices of systolic or diastolic function across GFR groups. After adjustment for potential confounders, reduced GFR was associated with increased AI, but not with decreased E/A or E’.

Conclusions: Early renal impairment may be partly associated with increased aortic stiffness, but not with LV systolic or diastolic function in CAD patients. (Circ J 2009; 73: 1740–1745)

Key Words: Aortic stiffness; Diastole; Kidney; Left ventricular hemodynamics; Systole

Although early stages of chronic kidney disease (CKD) are associated with increased risk for subsequent cardiovascular events, including death, worsening heart failure, recurrent myocardial infarction (MI), in patients with coronary artery disease (CAD),¹ the mechanisms underlying the association remain to be fully elucidated. Traditional cardiovascular risk factors, including age, hypertension and diabetes, account only in part for the association.²

End-stage renal disease is associated with a variety of alterations in cardiac structure and function, including left ventricular (LV) dilatation and hypertrophy and LV systolic and diastolic dysfunction.³ ⁴ Only a small number of new dialysis patients have normal cardiac morphology and function. Furthermore, aortic stiffness is increased in patients with end-stage renal disease.⁵ ⁶ As aortic stiffness increases, aortic pulse wave velocity increases and thereby the reflected waves from the periphery arrive earlier in the ascending aorta.⁷ Early return of the reflected waves augments the pressure in late systole and decreases the pressure in diastole, thereby increasing LV afterload and compromising coronary perfusion. These alterations aggravate myocardial ischemia and thus may further deteriorate LV dysfunction.

In the present study, we hypothesized that increased aortic stiffness and LV dysfunction may occur even in the early stages of CKD. To test the hypothesis, we examined the relation of estimated glomerular filtration rate (GFR) with the augmentation index (AI) of ascending aortic pressure and indices of LV systolic and diastolic function in patients who underwent cardiac catheterization for the evaluation of CAD.

Methods

Patients
We studied 359 consecutive patients who underwent left-sided cardiac catheterization for the evaluation of CAD and LV hemodynamics. All the patients had symptoms suggestive of angina and/or clinical signs of CAD, including positive exercise ECG, abnormal myocardial perfusion scintigram, and a previous history of MI or coronary revascularization. No patients with acute coronary syndrome, decompensated heart failure, thoracic aortic aneurysm, atrial fibrillation, primary valvular diseases, idiopathic dilated or hypertrophic cardiomyopathy, congenital heart disease or end-stage renal disease on maintenance hemodialysis were included. A history of hypertension, diabetes, MI, and coronary revascularization and medication status were determined by review of medical records. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg measured by indirect arm-cuff sphygmomanometry at rest or use of antihypertensive drugs. Diabetes was defined as a fasting blood glucose level >126 mg/dl or treatment with dietary modification, insulin, or oral hypoglycemic agents. All the patients had

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Table 1. Clinical Features of the Patient Subgroups

<table>
<thead>
<tr>
<th>GFR, ml-min⁻¹·1.73 m⁻²</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 (n=112)</td>
<td>60–75 (n=142)</td>
</tr>
<tr>
<td>Age, years</td>
<td>69.4±7</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>90 (80)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.7±2.8</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>55 (49)</td>
</tr>
<tr>
<td>Diabetics, n (%)</td>
<td>37 (33)</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>68 (61)</td>
</tr>
<tr>
<td>Prior coronary revascularization, n (%)</td>
<td>64 (57)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.08±0.18</td>
</tr>
<tr>
<td>GFR, ml-min⁻¹·1.73 m⁻²</td>
<td>51.1±7.1</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>51 (45)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>ACEI or ARB, n (%)</td>
<td>55 (49)</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>48 (43)</td>
</tr>
<tr>
<td>Calcium blocker, n (%)</td>
<td>47 (42)</td>
</tr>
<tr>
<td>Nitrate, n (%)</td>
<td>58 (52)</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>28 (25)</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>54 (48)</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation or frequency (within-group percentage).
*Diseased coronary artery was defined as major epicardial artery with ≥75% on the angiogram.
GFR, glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

Cardiac Catheterization
Ascending aortic and LV pressures were recorded as previously reported.8–10 Briefly, before contrast material was injected into the LV or coronary artery, ascending aortic and LV pressure waves were obtained with a catheter-tipped micromanometer (SPC-454D, Millar Instrument Company, Houston, TX, USA) and recorded on a polygraph system (RMC-2000, Nihon Kohden, Inc, Tokyo, Japan). From the recorded aortic pressure waves, the AI was calculated as augmented pressure divided by pulse pressure. From the recorded LV pressure waves, end-diastolic pressure (EDP), an index reflecting LV distensibility, and a time constant of decrease in LV pressure (Tau), an index of early diastolic relaxation, were determined as described elsewhere.11 The median values of measurements of 3 consecutive beats were used for statistical analyses. LV end-systolic and end-diastolic volumes were obtained from biplane left ventriculography using the method proposed by Chapman et al12 and were used for calculating the ejection fraction (EF). These volumes were corrected for body surface area.

Echocardiography
The day before the index cardiac catheterization, Doppler echocardiographic examination was performed (APLIO 80, Toshiba, Tokyo, Japan). Tissue Doppler imaging was obtained from the lateral mitral annulus. Mitral inflow and anular velocities were determined as the median values of measurements of 3 consecutive beats. LV mass was calculated from M-mode echocardiographic measurements13 and was corrected for body surface area.

Blood Sampling
The day before the index cardiac catheterization, complete blood count and blood chemistry were obtained for assessment of clinical features. The serum creatinine levels were determined by an enzymatic assay method (Kainos CRE-L kit, Kainos, Tokyo, Japan). GFR was estimated by the following equation proposed by the Japanese Society of Nephrology (http://www.jsn.or.jp/): GFR (ml-min⁻¹·1.73 m⁻²)=194×(serum creatinine level)⁻¹.094×age⁻⁰.287 (×0.739 if female).

Statistical Analysis
We used the SAS program package (SAS Institute, Cary, NC, USA) for all statistical analyses. We assessed linear trends across GFR groups using linear regression for continuous variables and the Mantel-Haenszel χ² test for categorical variables. For the AI and indices of LV systolic and diastolic function, we adjusted mean values for the variables that showed linear trends across GFR groups and assessed linear trends across GFR groups using linear regression. For the AI, we also adjusted mean values for variables that showed univariate predictive value for the AI in linear regression and assessed linear trends across GFR groups using linear regression. To assess whether the association between the GFR and AI is independent of hemodynamic parameters, multivariate linear regression was performed. Because of the collinearity between heart rate and mean aortic pressure (r=0.23, P<0.001), these variables were included separately in the multivariate models. The association between continuous variables was determined by Pearson’s correlation analysis. P<0.05 was considered significant.

Results
Clinical Features Stratified by GFR
Clinical characteristics of patients stratified according to GFR of 60, 75 and 90 ml-min⁻¹·1.73 m⁻² are shown in Table 1. Reduced GFR was associated with an increase in age and higher rates of prior revascularization and use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), calcium blockers, and diuretics. Hemodynamic and Doppler echocardio-
graphic features of patients stratified by GFR are shown in Table 2. There were progressive increases in the AI as well as central systolic pressure, pulse pressure and augmented pressure and decreases in a ratio of peak early to late diastolic mitral inflow velocities (E/A) and peak early diastolic mitral annular velocity (E’) with decreasing GFR. There were no linear trends in other indices of diastolic function (Tau, EDP or E/E’) or indices of systolic function (EF or peak systolic mitral annular velocity (S’)) across GFR groups.

### Adjusted Mean Values of the AI and Indices of LV Systolic and Diastolic Function Across GFR Groups

After adjustment for the variables that showed linear trends across GFR groups, including age, prior revascularization, and use of ACE inhibitors or ARBs, calcium blockers, and diuretics, reduced GFR was associated with increased AI (adjusted mean ± SE: 0.422 ± 0.012 in the group with GFR <60 ml·min⁻¹·1.73 m⁻², 0.411 ± 0.011 in the group with GFR 60–75 ml·min⁻¹·1.73 m⁻², 0.399 ± 0.016 in the group with GFR 75–90 ml·min⁻¹·1.73 m⁻², and 0.373 ± 0.021 in the group with GFR >90 ml·min⁻¹·1.73 m⁻²; P for trend < 0.05) but not with reduced E/A (adjusted mean ± SE: 0.80 ± 0.04 in the group with GFR <60 ml·min⁻¹·1.73 m⁻², 0.80 ± 0.03 in the group with GFR 60–75 ml·min⁻¹·1.73 m⁻², 0.81 ± 0.04 in the group with GFR 75–90 ml·min⁻¹·1.73 m⁻², and 0.87 ± 0.06 in the group with GFR >90 ml·min⁻¹·1.73 m⁻²; P for trend > 0.1) or E’ (adjusted mean ± SE: 9.2 ± 0.3 cm/s in the group with GFR <60 ml·min⁻¹·1.73 m⁻², 8.7 ± 0.3 cm/s in the group with GFR 60–75 ml·min⁻¹·1.73 m⁻², 9.0 ± 0.4 cm/s in the group with GFR 75–90 ml·min⁻¹·1.73 m⁻², and 8.6 ± 0.6 cm/s in the group with GFR >90 ml·min⁻¹·1.73 m⁻²; P for trend > 0.1). Similar adjustment did not change the lack of association of GFR with EF, S’, Tau, EDP, or E/E’ (all P for trend > 0.1).

In the univariate linear regression analysis, among the clinical and hemodynamic variables, significant predictive value for the AI was observed in GFR (r = −0.15, P < 0.01), age (r = 0.19, P < 0.01), hypertension (r = 0.19, P < 0.01), diabetes (r = −0.12, P < 0.05), prior revascularization (r = 0.12, P < 0.05), use of calcium blockers (r = 0.11, P < 0.05), use of β-blockers (r = 0.16, P < 0.01), heart rate (r = −0.34, P < 0.001), mean aortic pressure (r = 0.32, P < 0.001) and LV end-diastolic volume index (r = 0.14, P < 0.01). Even after adjustment for these variables, reduced GFR was associated with increased AI (adjusted mean ± SE: 0.422 ± 0.011 in the group with GFR <60 ml·min⁻¹·1.73 m⁻², 0.410 ± 0.010 in the group with GFR 60–75 ml·min⁻¹·1.73 m⁻², 0.396 ± 0.014 in the group with GFR 75–90 ml·min⁻¹·1.73 m⁻², and 0.382 ± 0.019 in the group with GFR >90 ml·min⁻¹·1.73 m⁻²; P for trend < 0.05).

In the multivariate linear regression model for AI that included GFR and heart rate, reduced GFR was an independent determinant of AI (standardized correlation coefficients for GFR and heart rate, −0.14 and −0.34, P < 0.01, respectively). In another multivariate linear regression model for AI that included GFR and mean aortic pressure, GFR was an independent determinant of AI (standardized correlation coefficients for GFR and mean aortic pressure, −0.14 and 0.31, P < 0.01 and P < 0.001, respectively).

### Correlation Between AI, Indices of LV Systolic and Diastolic Function, LV Mass and the Severity of CAD

The AI correlated significantly with indices of LV diastolic function (correlation coefficients for Tau, EDP, E’ and E/E’=0.23, 0.21, −0.24 and 0.23, respectively; All P < 0.001) and marginally with the LV mass index (r = 0.14, P = 0.06). The AI correlated with S’ (r = −0.22, P = 0.01), but not with EF (P = 0.1). It did not correlate with the number of major epicardial coronary arteries with 75% or more stenosis on angiography.

Significant but modest correlations were observed between LV diastolic function indices determined by cardiac catheterization and those determined by Doppler echocardiography; Tau correlated with E/A (r = 0.20, P < 0.001),
E’ (r=−0.28, P<0.001) and E/E’ (r=0.29, P<0.001) and EDP correlated with E/A (r=0.29, P<0.001), E’ (r=−0.10, P=0.08) and E/E’ (r=0.19, P<0.05).

Discussion

Major Findings
The major findings of the present study are that early renal insufficiency may be partly associated with increased aortic stiffness, but not with LV systolic or diastolic dysfunction, in patients with CAD.

Comparison With Earlier Studies
In contrast to accumulating evidence for an association between end-stage renal disease and a variety of alterations in cardiac structure and function,3,4 the relationship between early renal impairment and cardiac alterations has been less clear. Specifically, the echocardiographic substudy of the VALsartan In Acute myocardial Infarction trial (The VALIANT Echo Study)14 examined the relationship of renal function with LV systolic and diastolic function in 603 MI patients with serum creatinine levels <2.5 mg/dL. The study observed that estimated GFR did not correlate with EF or the transmural Doppler indices of diastolic function. The results on the effect of renal insufficiency on diastolic function in the VALIANT Echo Study, however, are inconclusive because the mitral inflow parameters are highly dependent on LV load15 and thus are less reliable measures of diastolic function. The present study is significant in showing the absence of a direct effect of renal insufficiency not only on E’, a relatively load-independent diastolic parameter, but also on invasively-assessed indices of diastolic function.

Several recent studies have reported an association of early renal impairment with increased aortic stiffness evaluated by aortic pulse wave velocity in hypertensives,16,17 CKD patients18,19 and the general population.20 Some of those studies, however, observed no significant correlation of GFR with a non-invasively determined AI.16,18,20 Although most indices of central aortic pressures and waveforms can be reliably estimated from radial waveforms with the use of the transfer function between aortic and radial pressures, the AI derived from this technique may be inaccurate.21 To our knowledge, the present study is the first to demonstrate the association of renal insufficiency with an elevated AI calculated from directly-measured aortic pressure waveforms in CAD patients.

Our results should be compared with those of a recent study by Edwards et al.22 They reported that aortic distensibility evaluated by magnetic resonance imaging and E’ were both reduced in stage 2 or 3 non-diabetic CKD patients without overt cardiovascular disease compared with age- and sex-matched healthy subjects.22 In the present study, E’ decreased with reducing GFR, but after adjustment for potential confounders, the association of E’ with GFR did not remain significant.

Consistent with recent studies using Doppler echocardiography, our study shows an association of increased aortic stiffness with impaired LV diastolic function. Specifically, Borlaug et al reported that increased late-systolic load, including elevated AI, was associated with slow LV relaxation assessed by E’ but not with EF in untreated hypertensives.23 Similarly, Eren et al reported that there was a progressive decrease in aortic distensibility with increasing grade of diastolic dysfunction determined by transmural Doppler measurements in patients with hypertension, diabetes or both.24 Our study confirms those findings and extends them by demonstrating the deleterious effect of increased aortic stiffness on invasively-determined LV diastolic relaxation and distensibility in CAD patients.

Possible Mechanisms
Although our observed association of reduced renal function with increased aortic stiffness may reflect shared underlying risk factors, including age and hypertension, there appear to be other mechanisms. First, reduced renal function may accelerate aortic stiffness. A prospective cohort study reported that high serum creatinine levels were the major determinant of accelerated progression of aortic stiffness over a 6-year period in treated hypertensives.25 Furthermore, increased aortic stiffness of patients with chronic renal failure has been reported to be improved after successful renal transplantation.26 The potential pathophysiological mechanisms by which renal dysfunction increases aortic stiffness include the detrimental effect of oxidative stress and inflammation,27 as well as elevated plasma levels of asymmetric dimethylarginine28 and homocysteine.29 seen even in mild-to-moderate renal dysfunction, on endothelial function.30

Alternatively, increased aortic stiffness may reduce renal function. An experimental study using the in vitro perfused hydro nephritic rat kidney demonstrated that elevated systolic pressure, a surrogate of increased aortic stiffness, rather than mean pressure, reduced renal blood flow by activating myogenic vasoconstriction of the renal afferent arteriole.31 Furthermore, in the remnant kidney model of chronic renal disease, the degree of hypertension-dependent glomerular injury correlated remarkably with systolic blood pressure.32,33 These observations suggest the deleterious effect of increased aortic stiffness on intra-renal hemodynamics and may partially explain the stronger predictive value of increases in systolic and pulse pressure rather than mean pressure for progressive deterioration of renal function.24

Study Strengths and Limitations
The major strengths of the present study include the use of a catheter-tipped micromanometer for recording the LV pressure wave for assessment of LV diastolic function. Although tissue Doppler echocardiography has been widely used for assessment of diastolic function, it represents the best available non-invasive assessment of diastolic function. Using a micromanometer catheter enabled us to determine the rapidly changing pressures that occur during LV isovolumetric relaxation34 and to determine a time constant of decrease in LV pressure, a gold index of early diastolic relaxation, and we demonstrated the absence of an association between reduced renal function and impaired LV diastolic relaxation and also showed the adverse effect of increased aortic stiffness on LV relaxation.

There are several potential limitations of the present study. First, we estimated the GFR using an equation that has been developed and validated in the Japanese population. Nevertheless, when we calculated the GFR using the 4-component Modification of Diet in Renal Disease (MDRD) equation36 or the Cockcroft-Gault equation,37 reduced GFR was associated with increased AI (correlation coefficients for GFRMDRD and GFRCOCK, -0.14 and −0.25, P<0.05 and P<0.01, respectively). Second, we do not have data on regional LV deformation. A recent study reported that regional systolic deformation assessed by strain/strain rate...
imaging was abnormal in early CKD patients without cardiovascular disease, despite normal EF and S. Third, our study cohort was a selected group of patients who were scheduled for cardiac catheterization for CAD and therefore could be considered to be at high risk for ischemic CAD. Our results can not be extended to general CAD patients. Furthermore, the degree of renal dysfunction in our study cohort is relatively mild, so our findings are not applicable to CAD patients with more severe renal insufficiency. Finally, a causal relationship between renal dysfunction and increased aortic stiffness could not be determined because of the cross-sectional nature of the present study.

Clinical Implications
A combination of reduced renal function and increased aortic stiffness in CAD patients is of particular clinical importance. Increased aortic stiffness increases LV afterload, slows LV relaxation and compromises coronary perfusion and thereby may contribute to the development of heart failure and myocardial ischemia. Furthermore, reduced renal function is frequently associated with limited capacity for volume control, which may also contribute to worsening symptoms of heart failure and angina pectoris. Thus, the combination of increased aortic stiffness and renal dysfunction in CAD patients presents a critical management challenge that has not been specifically addressed in any of the guidelines. Future studies should focus on mechanisms underlying interrelationships between cardiac, aortic and renal function, and the establishment of effective therapies to intervene in the unfavorable cardio-aorto-renal coupling.

Disclosure
None.

References


