Title	A reduction of coronary flow reserve is associated with chronic kidney disease and long-term cardio-cerebrovascular events in patients with non-obstructive coronary artery disease and vasospasm
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Citation	Fukushima Journal of Medical Science. 58(2): 136-143
Issue Date	2012
URL	http://ir.fmu.ac.jp/dspace/handle/123456789/341
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DOI	10.5387/fms.58.136
Text Version	publisher

Fukushima J. Med. Sci.,
Vol. 58, No. 2, 2012

[Original Article]

A REDUCTION OF CORONARY FLOW RESERVE IS ASSOCIATED WITH CHRONIC KIDNEY DISEASE AND LONG-TERM CARDIO-CEREBROVASCULAR EVENTS IN PATIENTS WITH NON-OBSTRUCTIVE CORONARY ARTERY DISEASE AND VASOSPASM

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(Received March 5, 2012, accepted June 13, 2012)

Abstract : Background : Coronary flow reserve (CFR) provides essential information about the coronary microvasculature. Chronic kidney disease (CKD) is a risk factor for cardio-cerebrovascular diseases. We hypothesized that low CFR is associated with CKD and long-term cardio-cerebrovascular events in the patients without obstructive coronary artery diseases and vasospasm.

Method and Results : In this study, 73 patients suspected with coronary artery disease but had no epicardial coronary stenosis and vasospasm were enrolled. There were 13 CKD patients and CFR was measured using the Doppler flow wire methods in the left anterior descending artery. CFR was significantly lower in CKD group than non-CKD group (3.13±0.6 vs. 4.00±1.1, $P=0.007$). From multivariate logistic regression analysis, the independent factor associated with the presence of CKD was only CFR (odds ratio 3.85, 95% confidence interval 1.27-11.70, $P=0.017$). In the patients with low CFR (≤2.8), cardio-cerebrovascular events were more common than those with normal CFR (CFR >2.8). Besides, in the patients who had both low CFR and CKD, long-term cardio-cerebrovascular events were more likely to occur than those with normal CFR or non-CKD.

Conclusions : Our data suggest that low CFR is associated with CKD and cardio-cerebrovascular events in the patients without coronary stenosis and vasospasm.

Key words : coronary flow reserve (CFR), doppler flow wire, coronary microcirculation, chronic kidney disease (CKD), cardio-cerebrovascular event

INTRODUCTION

Approximately 10% to 30% of patients who had angina-like chest pain referred for cardiac catheterization are found to have either normal coronary arteries or only a minimal degree of atherosclerosis[1-3]. Some of those patients are found to have other forms of heart disease such as hypertrophic cardiomyopathy and coronary artery spasm. Coronary flow reserve (CFR) provides essential information about the coronary microvascular bed in the absence of narrowing of epicardial coronary arteries. Impairment of CFR may result from vasomotor, metabolic or structural abnormalities in

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the coronary microcirculation and may precede coronary atherosclerosis[4].

Not only severe renal disease, mild renal disease is accompanied by increased cardiovascular risk and mortality[5-8]. Besides, it has been also reported that the renal dysfunction increased the risk of cerebral infarction[9]. Glomerular filtration rate (GFR) may in part reflect and rely on the integrity of the renal microvascular bed. Although it has been reported that microvascular dysfunction is a systemic disorder that might cause parallel deleterious alterations in both the coronary and the renal microvasculature at early stages[10], the pathophysiological mechanisms between CFR and renal dysfunction remain to be fully elucidated. Besides, although several studies reported that reduction in CFR may be associated with increased cardiovascular mortality in patients with normal coronary arteries[11-13], the association with CFR and cerebrovascular event, especially in the presence of CKD, was unclear.

The aim of the present study was to assess the relationships between CFR and chronic kidney disease (CKD), and the long-term cardio-cerebrovascular event of CFR response in patients without epicardial coronary stenosis and vasospasm.

METHODS

Study protocol was approved by the institutional review board. Informed consent was obtained from all patients in this study.

Study population: The patients who suspected coronary artery disease but had no obstructive coronary artery disease and vasospasm estimated by control coronary arteriography (CAG) and coronary spasm provocation test, were enrolled in the present study. After exclusion of patients with moderate to severe valvular disease, left ventricular ejection fraction (LVEF) of less than 50% by echocardiography, previous myocardial infarction, cerebral infarction and hypertrophic or dilated cardiomyopathy, 73 patients were examined for the assessment of CFR from 1993 to 2008 (mean age, 62.7±9.3 years). To allow the assessment of coronary physiology at baseline, calcium channel-blocking agents, long-acting nitrates and β-blocker were withheld at least 48 hours before CAG and CFR measurement.

We also assessed coronary risk factors, including a history of smoking, hypertension, dyslipidemia and diabetes mellitus. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and/or under antihypertensive treatment. Dyslipidemia was defined as total cholesterol ≥220 mg/dl, fasting triglycerides ≥150 mg/dl or under lipid-lowering treatment. Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dl, postprandial blood glucose ≥200 mg/dl, and/or under glucose-lowering treatment.

Assessment of renal function: We calculated the estimated GFR (eGFR) from age and serum creatinine (Scr) using the Japanese GFR estimation equation proposed by the Japanese Society of Nephlogy as follows: $eGFR = 194 \times Scr^{-1.094} \times age^{-0.287}$ (if female, $\times 0.739$)[14]. The presence or absence of CKD was defined by using the cut-off of 60 ml/min/1.73 m^2 as the lower limit of eGFR for normal renal function[15]. The patients were subsequently divided into two groups, CKD group and non-CKD group, according to their renal functions as assessed by eGFR just in prior to CAG.

Study protocol and measurement of CFR: Diagnostic CAG was performed using 5Fr. or 6Fr. Judkins catheter with a standard femoral percutaneous approach. Heparin sodium (3,000 units) was administered intravenously at the beginning of the procedure. If there was no significant epicardial coronary stenosis by control CAG and coronary vasospasm was not evoked by the two to three doses of intracoronary administration of acetylcholine (25, 50 and 100 μg for the left coronary artery; 25 and 50 μg for the right coronary artery, for 30 seconds each), CFR was then assessed. The coronary spasm provocation test was considered positive when an ischemic electrocardiogram changes and/or chest pain with coronary constriction was induced by intracoronary administration of acetylcholine, based on the 2008 Guidelines of the Japanese Circulation Society[16]. For the assessment of CFR, first, a 0.014 inch Doppler guide wire (Volcano, Rancho Cordova, CA, USA) was placed in the proximal portion of the left anterior coronary (LAD) artery to measure the average peak flow velocity [APV (cm/second)] of the coronary artery. Second, by intracoronary nitroglycerin (2.5 mg bolus) administration, the epicardial portion of the left coronary artery was kept maximally dilated, following which papaverine (12 mg for 10 seconds) was administered into the left coronary artery through the same guiding catheter. Thus, the change in APV in response to intracoronary papaverine was considered as CFR to reflect the coronary microvascular function. We performed this protocol as described previously[17].

Catamnestic follow-up: In May 2009, the patient's information was obtained by regular contacts with family doctors, and by telephone contacts with patients or patient families. The patients were prospectively followed-up to register cardiovascular events for on average follow-up period of 8.4±4.3 years.

Statistical analysis: Results are presented as mean±standard deviation (SD) values for continuous variables and as the percentage of total patients for categorical variables. Unpaired Student *t* test and Fisher's exact probability test were used for comparisons of continuous and categorical variables between 2 groups, respectively. If data were not distributed normally, the Mann-Whitney *U* test was used. Correlation between CFR and eGFR was studied with the Pearson's correlation test. Logistic regression analysis was employed to calculate odds ratio (OR) and their 95% confidence intervals (CI). Event-free survival was examined by Kaplan-Meier method and analyzed by a log-rank test. A value of $P<0.05$ was considered significant. All analyses were performed using StatView version 5 for windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Clinical characteristics of study subjects: All patients included in this study had no epicardial coronary artery stenosis and vasospasm, and they were divided into two groups according to their renal function as assessed by eGFR. There were 13 patients in CKD group and 60 patients in non-CKD group in this study. The main clinical baseline characteristics data grouped by eGFR are presented in Table 1. Mean eGFR was 49.5 ± 11.2 ml/min/1.73 m^2 in CKD group and 78.7 ± 14.0 ml/min/1.73 m^2 in non-CKD group. CFR was significantly lower in CKD group than non-CKD group (3.13±0.6 vs. 4.00±1.1, $P=0.007$). Although the patients in CKD group were more likely to be older than those in non-CKD group, there were no significant differences in gender between the two groups. Table 1 also shows no significant difference between the two groups with respect to the prevalence of cardio-cerebrovascular and/or renal risk factors (i.e. hypertension, dyslipidemia, diabetes mellitus and smoking). Besides, LVEF assessed by echocardiography was similar for the both groups.

Relationship between CFR value and eGFR: Patients with CKD group had significantly lower CFR than patients with non-CKD group (Table 1), and CFR was correlated with eGFR ($R=0.48$, $P<0.0001$) as shown in Figure 1. Univariate logistic regression analysis revealed that the presence of CKD was significantly associated with CFR and age. Multivariate logistic regression analysis revealed that independent factor associated with the presence of CKD was only CFR (Table 2, OR 3.85, 95% CI 1.27-11.70, $P=0.017$).

Prognostic value of CFR: There were total of 10 cardio-cerebrovascular events during follow-up periods (2 of cardiac sudden death, 5 of acute coronary syndrome and 3 of cerebral infarction). The best cut-off value of CFR to predict cardio-cerebrovascular events was 2.8 from receiver operating curve (ROC), and the value of CFR ≤2.8 had 40% sensitivity and 87.5% specificity to detect patients with these events (area under ROC=0.564). There were 12 low CFR (≤2.8) patients in this study and

Table 1. Characteristics of patients

		CKD ($n=13$)	non-CKD ($n=60$)	*P* value
Age	(year)	68.3 ± 6.9	61.5 ± 9.3	0.015
Male	(n, %)	5 (38.5)	32 (53.3)	n.s.
eGFR	ml/min/1.73 m^2	49.5 ± 11.2	78.7 ± 14.0	–
CFR		3.13 ± 0.6	4.00 ± 1.1	0.007
LVEF	(%)	63.9 ± 9.4	63.0 ± 8.3	n.s.
Hypertension	(n, %)	8 (61.5)	25 (41.7)	n.s.
Dyslipidemia	(n, %)	3 (23.1)	14 (23.3)	n.s.
Diabetes mellitus	(n, %)	2 (15.4)	4 (6.7)	n.s.
Smoking	(n, %)	2 (15.4)	9 (15.0)	n.s.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CFR, coronary flow reserve; LVEF, left ventricular ejection fraction, n.s.; not significant.

Table 3 shows logistic regression analysis for low CFR. Univariate logistic regression analysis revealed that the presence of low CFR was significantly associated with age, CKD and the presence of diabetes mellitus. Multivariate logistic regression analysis revealed that independent factors associated with low CFR were the presence of CKD and diabetes mellitus. Figure 2 shows Kaplan-Meier event-free curves for cardio-cerebrovascular events in low CFR patients and normal CFR patients. Normal CFR patients had better outcome than low CFR patients ($P=0.033$ by log-rank test).

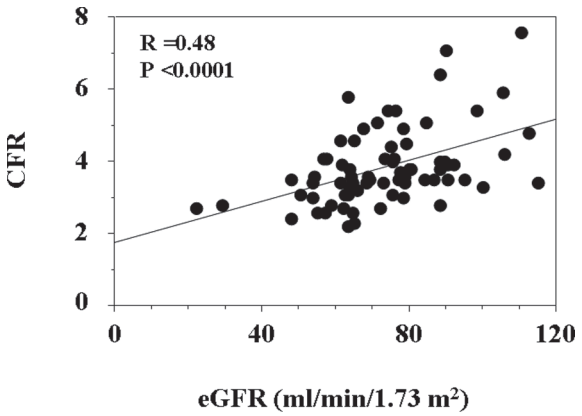

Fig. 1. The correlation between CFR value and eGFR. CFR was positively correlated with eGFR.
CFR, coronary flow reserve ; eGFR, estimated glomerular filtration rate.

Prognostic value of CKD patients : There were 4 patients in CKD group and 6 patients in non-CKD group with cardio-cerebrovascular events. The event rate was significantly higher in CKD group than non-CKD group (30.8% vs. 10.0%, $P=0.048$). Kaplan-Meier event-free curves for cardio-cerebrovascular events in CKD and non-CKD groups are shown in Figure 3. Patients with non-CKD group had better outcome compared to those with CKD group ($P=0.0008$ by log-rank test). Table 4 shows comparisons of clinical characteristics between the patients with or without cardio-cerebrovascular events in CKD group. There were no statistically significant differences in age,

Table 2. Univariate and multivariate logistic regression analyses to predict the presence of CKD

	Univariate	analysis	Multivariate	analysis
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (y)	1.11 (1.02-1.22)	0.022	0.91 (0.82-1.00)	0.054
Sex (female)	1.83 (0.54-6.24)	0.335		
CFR	4.41 (1.46-13.33)	0.026	3.85 (1.27-11.70)	0.017
LVEF	0.99 (0.92-1.06)	0.727		
Hypertension	2.24 (0.66-7.66)	0.199		
Dyslipidemia	0.99 (0.24-4.09)	0.984		
Diabetes mellitus	2.55 (0.41-15.66)	0.313		
Smoking	1.03 (0.20-5.45)	0.972		

OR, odds ratio ; CI, confidence interval.

Table 3. Univariate and multivariate logistic regression analyses to predict low CFR (≤2.8)

	Univariate	analysis	Multivariate	analysis
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (y)	1.11 (1.01-1.21)	0.035	1.04 (0.94-1.15)	0.412
Sex (female)	1.55 (0.44-5.41)	0.496		
CKD	7.71 (1.94-30.62)	0.004	6.68 (1.36-32.94)	0.020
LVEF	1.00 (0.93-1.08)	0.986		
Hypertension	1.26 (0.37-4.35)	0.715		
Dyslipidemia	0.26 (0.03-2.14)	0.209		
Diabetes mellitus	14.75 (2.32-93.92)	0.004	11.95 (1.44-98.98)	0.021
Smoking	1.16 (0.22-6.17)	0.866		

gender, eGFR, LVEF and prevalence of cardio-cerebrovascular and/or renal risk factors between the patients with and without events in CKD group. However, CFR was lower in the patients with events than those without events in CKD group (2.60±0.2 vs. 3.37±0.5, $P=0.016$).

Prognostic value of both low CFR and CKD patients : Kaplan-Meier event-free curves for cardio-cerebrovascular events in the patients with both of low CFR and CKD are shown in Figure 4. In this study, there were 6 patients who had both low CFR and CKD. Among these, 4 patients had cardio-cerebrovascular events. The data showed that the patients with both of low CFR and CKD had worse outcome ($P<0.0001$ by log-rank test).

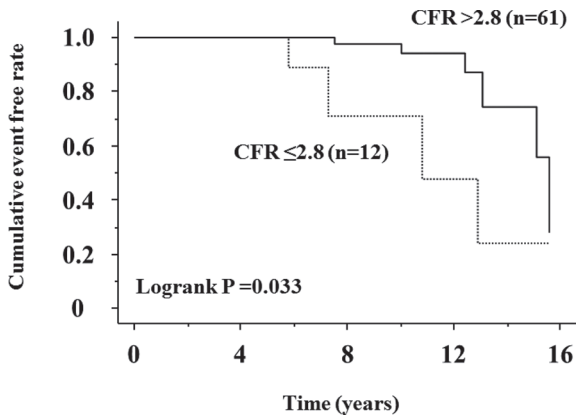

Fig. 2. Kaplan-Meier event-free curves (considering cardio-cerebrovascular events as an end point) in patients stratified according to low (≤2.8) or normal (>2.8) CFR at Doppler flow wire method. There were total of 10 cardio-cerebrovascular events during follow-up periods in this study. Event-free rate with a CFR >2.8 was significantly different from that with a CFR ≤2.8 ($P=0.033$).

DISCUSSION

CFR is an integrating measure of endothelial function when there were no epicardial coronary stenoses[18,19]. Renal functional impairment was also associated with markers of endothelial dysfunction[20], and renal dysfunction was a short-term and long-term independent predictor of mortality[21-23]. There were a few studies to compare coronary microvascular function with renal function. Chade *et al.* showed that reduced renal function is associated with attenuated coronary vasodilator capacity in patients without obstructive coronary artery disease[10]. However, they found that differences in age, sex and prevalence of hypertension were largely responsible for the observed differences in CFR. Koivuviita *et al.* demonstrated that there was

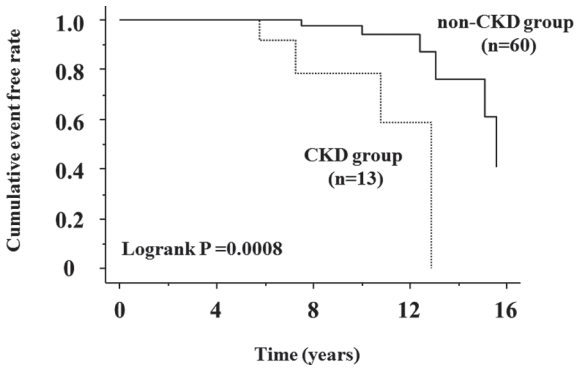

Fig. 3. Kaplan-Meier event-free curves (considering cardio-cerebrovascular events as an end point) in patients stratified according to CKD or non-CKD assessed by eGFR. Event-free rate with a CKD was significantly different from that with a non-CKD ($P=0.0008$).
CKD, chronic kidney disease.

Table 4. Clinical characteristics between the patients with cardio-cerebrovascular events and those without events in CKD group

		Event ($n=4$)	Event-free ($n=9$)	P value
Age	(year)	67.3 ± 3.4	68.8 ± 8.1	n.s.
Male	(n, %)	2 (50.0)	3 (33.3)	n.s.
eGFR	ml/min/1.73 m^2	54.7 ± 4.7	47.2 ± 12.7	n.s.
CFR		2.60 ± 0.2	3.37 ± 0.5	0.016
LVEF	(%)	65.5 ± 12.3	63.2 ± 8.6	n.s.
Hypertension	(n, %)	2 (50.0)	6 (66.7)	n.s.
Dyslipidemia	(n, %)	0 (0)	3 (33.3)	n.s.
Diabetes mellitus	(n, %)	1 (25.0)	1 (11.1)	n.s.
Smoking	(n, %)	1 (25.0)	1 (11.1)	n.s.

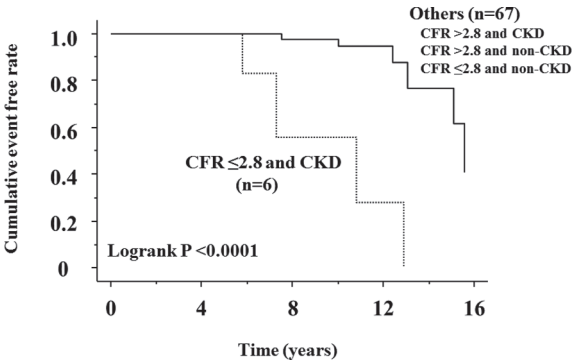

Fig. 4. Kaplan-Meier event-free curves (considering cardio-cerebrovascular events as an end point) in patients stratified according to both of low CFR and CKD, or the others. In this study, there were 6 patients with both of low CFR and CKD, and among these patients, there were 4 cardio-cerebrovascular events. Event-free rate with both of low CFR and CKD was significantly different from that with normal CFR or non-CKD ($P<0.0001$).

a trend toward low CFR with more significant CKD, but they did not find a significant association between CFR and CKD[24]. On the other hand, Bezante *et al.* showed even after adjustment for age and gender, the presence of CKD entailed a sevenfold higher of having impaired CFR[25], and Charytan *et al.* also examined low CFR may accelerate in mild to moderate CKD[26]. In our study, although patients with CKD group were older, there were no significant differences in gender and the prevalence of hypertension between CKD and non-CKD groups. The value of CFR was significantly lower in CKD group than non-CKD group. Besides, CFR correlated with eGFR and multivariate logistic regression analysis revealed that independent factor associated with the presence of CKD was only CFR. These results suggest that CFR is associated with CKD in the patients without obstructive coronary artery disease and vasospasm. In addition, although it is recently reported that low GFR is associated with vasospastic angina[27], all patients in this study were ruled out the possibility of vasospastic angina.

A reduction in CFR may play a role in the development of myocardial ischemia[11-13] and may be associated with increased cardiovascular mortality in patients with normal coronary arteries[28]. CKD is strongly associated with increased risk of cardiovascular disease[15,29,30]. Koren-Morag *et al.* described that about 1/5 of patients with coronary heart disease had chronic renal dysfunction[31]. In addition, Hao Z *et al.* reported that more than 1/4 of patients with acute cerebral infarction presented with renal dysfunction[32]. They also reported that reduced eGFR was independent predictor of death/disability at the end of the 12th month in patients with acute cerebral infarction. Thus, there were several reports that reduced CFR was associated with cardiovascular disease, and reduced eGFR was associated with cardio-cerebrovascular event, however, there was no report to reveal correlation with CFR and cerebrovascular events. In the present study, low CFR and/or CKD were associated with a high rate of long-term cardio-cerebrovascular events in the patients without obstructive coronary artery disease and vasospasm.

Microvascular dysfunction appears to be part of a systemic process[33,34]. The functional capacity of the myocardial microcirculation may be assessed by CFR, and GFR may in part reflect and rely on the integrity of the renal microvascular bed. Impairment in both microcirculatory beds may reflect an unmeasured risk factor induced by blunted renal function and add a burden to the increased propensity for vascular events in CKD[10]. Cerebrovascular events are also caused by the presence of microvascular dysfunction, and it is considered that similar histopathological changes in several vascular beds may occur nearly simultaneously[35-38]. From our study, it has possibilities that the existence of low CFR and GFR reflects not only coronary and renal arterial microvascular dysfunction, but also systemic microvasculature such as cerebral infarction.

Limitations: Our study has several limitations. 1) It was performed in a single center and small scale including 73 patients, which may not represent the whole Japanese population. 2) CFR was measured only in the LAD. There is no doubt that the 3-coronary approach would be more fruitful, but it remains technically challenging. 3) Doppler assessment of CFR has some limitations. For example, assessment of absolute blood velocity can be limited in some patients by the large incident angle between the Doppler beam and blood flow.

CONCLUSIONS

In conclusion, our data suggest that coronary microvascular dysfunction is associated with CKD. The presence of both of low CFR and CKD may be important predictors for cardio-cerebrovascular events in the patients without coronary stenosis and vasospasm.

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