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Cystatin C Versus Creatinine- Based Definition of Renal Dysfunction for Predicting Poor Coronary Collateralization in Type 2 Diabetic Patients with Stable Coronary Artery Disease

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Abstract

Objective: Renal dysfunction represents a risk factor for poor coronary collateral growth. We investigated whether Glomerular Filtration Rate (GFR) estimated with the cystatin C-based formula (GFR_{CYS}) is superior to that with the creatinine-based abbreviated Modification of Diet in Renal Disease (GFR_{MDRD}) and the Chronic Kidney Disease Epidemiology Collaboration (GFR_{EPI}) equations for evaluating coronary collateralization in type 2 diabetic patients with stable coronary artery disease.

Methods: GFR was estimated with creatinine- and cystatin C- based equations in 302 diabetic and 127 non-diabetic patients with stable angina and angiographic total occlusion of at least one major coronary artery. The degree of collaterals supplying the distal aspect of a total occlusion from the contra-lateral vessel was graded as poor (Rentrop score of 0 or 1) or good collateralization (Rentrop score of 2 or 3).

Results: In diabetic patients, GFR_{CYS} correlated more closely with Rentrop score than GFR_{MDRD} (Spearmen's r=0.44 vs. Spearmen's r=0.30, P=0.047) and GFR_{EPI} (Spearmen's r=0.44 vs. Spearmen's r=0.29, P=0.028), and area under the curve of GFR_{CYS} was larger compared with that of GFR_{MDRD} and GFR_{EPI} (0.78 vs. 0.68 and 0.66, P=0.001 and P<0.001) for predicting the presence of poor collateralization, along with a net reclassification improvement of 15.0% and 20.1% (P=0.025 and P=0.002). After adjusting for possible confounding variables, a GFR<90 mL/min/1.73m^2 estimated with the cystatin C- based formula was more independently associated with poor collateralization (OR:6.21 *vs.* 2.86 and 2.36, P=0.042 and P=0.015). In contrast, GFR_{CYS}, GFR_{MDRD}, and GFR_{EPI} were similar for assessing coronary collateralization in non-diabetic patients.

Conclusions: Cystatin C-based definition of renal dysfunction indicates a potential better clinical utility than creatinine-based equations for predicting poor Cystatin collaterals in diabetic atherosclerotic patients.

Keywords: Renal function; Diabetes; Coronary collateralization; Coronary artery disease; Stable angina; Chronic total occlusion

Introduction

Coronary collateral circulation offers an alternative source of blood supply to an ischemic region caused by transient or permanent occlusion of major coronary arteries [1,2]. Well-developed coronary collaterals contribute to a reduction of infarct size, preservation of left ventricular function, and an improvement of survival in patients with coronary artery disease [3,4]. Diabetes mellitus represents a powerful independent risk factor for the development of chronic kidney disease, diffuse coronary artery disease, and impaired physiological adaptive response of coronary collateralization [5-8]. Recent studies have shown that renal dysfunction is strongly associated with poor coronary collateral growth [9-11] and increased cardiovascular mortality [12], even when glomerular filtration rate (GFR) is mildly decreased [11,13], suggesting that early detection of renal dysfunction is particularly important in the management of diabetic patients with coronary artery disease.

Serum creatinine-based abbreviated Modification of Diet in Renal Disease (MDRD) equation is commonly used to estimate GFR [14], but it may lack accuracy to monitor kidney function in patients with early phase of renal impairment [15]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has been introduced as a better means to estimate GFR in observational research [16]. Cystatin C, which is produced by all nucleated cells at a constant rate and has been considered to be a native anti-angiogenic factor [17], is freely filtered across the glomerular membrane and not influenced by age, sex, muscle mass, exercise or diet [18]. Its serum level was used as an endogenous marker of renal function superior to serum creatinine [19-21]. However, data from diabetic patients with stable coronary artery disease comparing cystatin C- versus creatinine- based definition of renal dysfunction in the evaluation of coronary collateralization remain largely limited. In this study, we tested the hypothesis that GFR estimated with the cystatin C-based formula (GFR_{CYS}) is a better indicator of coronary collateralization compared with that using the creatinine-based MDRD (GFR_{MDRD}) and the CKD-EPI (GFR_{EPI}) equations in a unique cohort of type 2 diabetic patients with stable angina and chronic coronary total occlusion. This angiographic inclusion criterion of study patients was used because a severe coronary artery obstruction was a prerequisite for spontaneous collateral recruitment [22]. The presence and degree of coronary collateralization were assessed according to the

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Rentrop grading system [23] as this method is easy to incorporate into the routine clinical practice.

Methods

The research protocol was approved by the Institutional Review Board of Rui Jin Hospital, Shanghai Jiaotong University School of Medicine, and was registered (NCT02089360). Informed consents were obtained in written form from all patients, and clinical investigation was conducted according to the principle of the Declaration of Helsinki.

Study population

A total of 579 consecutive patients with stable angina and chronic total occlusion (>3 months) of at least one major epicardial coronary artery between January 2009 and October 2013 were screened. All patients were referred to coronary angiography because of chest pain on exertion. For the purpose of research, patients who received percutaneous coronary intervention within the prior 3 months (n=45) or had a history of coronary artery bypass grafting (n=43) were excluded. We also excluded patients with renal failure requiring hemodialysis (n=2) and those who had chronic heart failure, pulmonary heart disease, malignant tumor or immune system disorders (n=22). Thirty-two patients whose serum cystatin C measurements were not available and six patients with type 1 diabetes were excluded. The remaining 429 (302 diabetic and 127 non-diabetic) eligible patients were included in the final analysis.

Stable angina was diagnosed according to the criteria recommended by the American College of Cardiology/ American Heart Association [24]. The duration of coronary artery occlusion was estimated from the date of occurrence of myocardial infarction in the area of myocardium supplied by the occluded vessel, from an abrupt worsening of existing angina pectoris, or from information obtained from a previous angiogram. The diagnosis of type 2 diabetes mellitus and dyslipidemia was made according to the criteria of the American Diabetes Association and Third Report of The National Cholesterol Education Program (NCEP) [25,26].

Coronary angiography

Coronary angiography was performed through the femoral or radial approach [27]. All angiograms were reviewed by two experienced interventional cardiologists, according to lesion classification scheme of the American College of Cardiology/ American Heart Association [28]. They were blinded to study protocol and biochemical measurements, and any difference in interpretation was resolved by a third reviewer. Multivessel coronary disease was defined as the presence of ≥ 50% luminal diameter stenosis involving at least two major epicardial coronary arteries. The presence and degree of collaterals supplying the distal aspect of a total coronary occlusion from the contra-lateral vessel were graded on a 4-point scale from 0 to 3 according to the Rentrop scoring system [23]: zero=no collateral vessels; 1=thread-like, poorly opacified collaterals with faint visualization of the distal vessel; 2=moderately opacified collateral channels; 3=large, brightly filled collateral channels with immediate visualization of the entire distal vessel >10 mm. Patients were then classified as poor (Rentrop score of 0 and 1) and good (Rentrop score of 2 and 3) coronary collateralization, as in previous studies [5-9,12,13]. For those with more than one total coronary occlusion, the vessel with the highest collateral grade was chosen for analysis.

Biochemical measurement and estimation of GFR

Blood samples were collected at the day of angiography in all patients after an overnight fasting, and stored at -80°C until analysis. Serum glucose, glycosylated hemoglobin (HbA1c), creatinine, blood urea nitrogen, uric acid, and lipid profiles were determined with standard laboratory techniques [7,8]. Serum cystatin C was measured by high sensitive latex-enhanced immune-turbidimetric method with an automatic biochemical analyzer (7600-020; Hitachi Inc, Tokyo, Japan).

GFR was estimated with the following equations:

GFR_{MDRD} (mL/min/1.73 m^2) = [186.3 × creatinine$^{-1.354}$ (mg/dL) × age$^{-0.203}$ × 0.742 (if female)] [14,29];

GFR_{EPI} (mL/min/1.73 m^2) = 141 × min (creatinine/k, 1)$^{\alpha}$ × max (creatinine/k, 1)$^{-1.209}$ × 0.993^{age} × 1.018 [if female], where k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of creatinine/ k or 1, and max indicates the maximum of creatinine/ k or 1 [16,20];

GFR_{CYS} (mL/min/1.73 m^2) = [133 x cystatin C/0.8$^{-0.499}$ (mg/L) × 0.996^{age} × 0.932 (if female)], when serum cystatin C ≤ 0.8 mg/L, or

GFR_{CYS} (mL/min/1.73 m^2) = [133 × cystatin C/0.8$^{-1.328}$ (mg/L) × 0.996^{age} x 0.932 (if female)], when serum cystatin C > 0.8 mg/L [18].

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) or median (25th ~ 75th percentiles), and categorical data are summarized as frequencies or percentages. For categorical clinical variables, differences between groups were evaluated with the chi-square test followed by Bonferroni's correction to account for multiple comparisons. For continuous variables, the existence of a normal distribution was evaluated with the Kolmolgorov–Smirnov test. Non-normally distributed parameters were analyzed by log-transformation or non-parametric tests. Differences among groups were analyzed by One-Way Analysis Of Variance (ANOVA) or the Kruskal–Wallis analysis followed by post-hoc analysis. Correlation between GFR and Rentrop score was determined by the Spearman's rho test as appropriate. For illustration of the agreement of the two GFR definitions, an intraclass correlation and an inter-rater agreement kappa (κ) coefficient according to Fleiss-Cohen were calculated [30]. The independent determinants for poor collateralization were assessed by multivariate logistic regression analysis, and the covariates chosen to enter the multivariate analysis model included age, gender, body mass index (BMI), risk factors for coronary artery disease, multivessel disease, and renal impairment expressed by GFR_{MDRD} (mode 1), GFR_{EPI} (model 2) or GFR_{CYS} (model 3). Receiver-operating characteristic (ROC) curve was plotted to assess the power of GFR estimated with the cystatin C- or creatinine- based equations for detecting poor collateralization, and the area under the curve was compared using the DeLong method. Since the area under the curve has well-known limitations to detect an improvement of a risk score by an additional biomarker, even if it is strongly associated with the disease [31], the net reclassification and integrated discrimination improvements (NRI and IDI) were calculated by substituting GFR_{CYS} for GFR_{MDRD} or GFR_{EPI} according to coronary collateralization [32]. All analyses used 2-sided tests with an overall significance level of alpha=0.05, and were performed with the SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics

Baseline demographic and clinical characteristics and biochemical

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measurements are listed in Table 1. Diabetic and non-diabetic patients with poor collateralization were females in higher percentage but less hypertensive, and had more dyslipidemia than those with good collateralization (for all comparisons, $P<0.05$). Although higher serum levels of creatinine and cystatin C were associated with poor coronary collateralization, patients with diabetes and poor collateralization had lower creatinine and cystatin C levels than their non-diabetic counterparts.

Comparison between creatinine- and cystatin C- based GFR

For diabetic and non-diabetic patients, all GFR_{MDRD}, GFR_{EPI}, and GFR_{CYS} measurements were lower in those with poor collateralization (Table 1). Despite significant correlation between GFR_{MDRD}, GFR_{EPI}, and GFR_{CYS} (Figure 1), the cystatin C-based formula identified a quite different population with at least mild renal dysfunction defined as a GFR<90 mL/min/1.73 m^2 compared with the creatinine-based MDRD and CKD-EPI equations in diabetic (GFR_{MDRD}: 80 identical/96 not identical; κ=0.35 [95% CI 0.24 ~ 0.46]; GFR_{EPI}: 107 identical/92 not identical; κ=0.41 [95% CI 0.31 ~ 0.50]) and non-diabetic (GFR_{MDRD}: 38 identical and 34 not identical; κ=0.42 [95% CI 0.26 ~ 0.57]; GFR_{EPI}: 46 identical/37 not identical; κ=0.44 [95% CI0.30 ~ 0.58]) patients.

Risk for poor collateralization based on different GFR estimating equations

In diabetic patients, GFR_{CYS} correlated more closely with Rentrop score than GFR_{MDRD} (Spearman's r=0.44, $P<0.001$ vs. Spearman's r=0.30, $P<0.001$, Z statistics=2.00, P=0.047) and GFR_{EPI} (Spearman's r=0.44, $P<0.001$ vs. Spearman's r=0.29, $P<0.001$, Z statistics=2.00, P=0.046), after adjusting for age, gender, BMI, risk factors for coronary artery disease, and multivessel coronary disease. In non-diabetic patients, after adjusting for these confounding variables, GFR_{CYS} (Spearman's r=0.25, $P<0.001$) but not GFR_{MDRD} (Spearman's r=0.16, P=0.08) and GFR_{EPI} (Spearman's r=0.14, P=0.12) was significantly related to Rentrop score (Z statistics=0.77, P=0.44; Z statistics=1.00, P=0.32) (Figure 2).

ROC curve analysis showed that the area under the curve of GFR_{CYS} was larger compared with that of GFR_{MDRD} and GFR_{EPI} (0.78 vs. 0.68 and 0.66, both $P<0.001$), and the cut-off of GFR<90 mL/min/1.73 m^2 was more sensitive (74.6% vs. 67.8% and 57.6%) and specific (67.2% vs. 57.6% and 66.4%) with the cystatin C-based formula than that with the creatinine-based MDRD and CKD-EPI equations for predicting

Variables	Diabetes (n = 302)			Non-diabetes (n = 127)		
	Poor (n = 125)	Good (n = 177)	*P* value	Poor (n = 33)	Good (n = 94)	*P* value
Female, n (%)	41 (33.1)	33 (18.8)	0.005	11 (33.3)	14 (14.9)	0.02
Age, y	65.5 ± 9.8	64.0 ± 11.0	0.23	67.9 ± 10.0	63.6 ± 10.2	0.04
Body mass index, Kg/m^2	25.1 ± 3.5	24.8 ± 3.3	0.43	26.5 ± 3.0	24.9 ± 3.2	0.01
Smoke, n (%)	50 (40.0)	60 (33.9)	0.28	13 (39.4)	43 (45.7)	0.53
Hypertension, n (%)	77 (61.6)	133 (75.1)	0.01	18 (54.5)	69 (73.4)	0.045
Dyslipidemia, n (%)	70 (56.0)	75 (42.4)	0.02	20 (60.6)	34 (36.2)	0.02
Systolic blood pressure, mm Hg	137.5 ± 18.3	140.9 ± 16.5	0.09	139.5 ± 20.0	140.8 ± 21.1	0.75
Diastolic blood pressure, mm Hg	82.8 ± 10.5	85.0 ± 8.7	0.05	83.4 ± 13.3	83.9 ± 9.7	0.82
Fasting blood glucose, mmol/L	6.0 ± 2.0	5.7 ± 1.6	0.15	5.3 ± 0.7	5.0 ± 0.6	0.03
HbA1c, %	6.7 ± 1.3	6.5 ± 1.6	0.30	5.9 ± 0.3	5.8 ± 0.4	0.09
Severity of coronary artery disease, n (%)			0.10			0.68
1-vessel	29 (23.2)	26 (14.7)		5 (15.2)	11 (11.7)	
2-vessel	35 (28.0)	65 (36.7)		14 (42.4)	35 (37.2)	
3-vessel	61 (48.8)	86 (48.6)		14 (42.4)	48 (51.1)	
Triglyceride, mmol/L	1.9 ± 0.9	1.8 ± 1.3	0.37	1.8 ± 0.9	1.7 ± 0.9	0.63
Total cholesterol, mmol/L	4.5 ± 1.5	4.3 ± 1.2	0.29	3.9 ± 1.1	4.3 ± 1.2	0.16
HDL-cholesterol, mmol/L	0.99 ± 0.25	1.05 ± 0.29	0.04	0.93 ± 0.21	1.02 ± 0.25	0.07
LDL-choleterol, mmol/L	2.7 ± 1.2	2.5 ± 1.0	0.07	2.5 ± 1.0	2.7 ± 1.1	0.32
Blood urea nitrogen, mmol/L	5.5 ± 1.7	5.4 ± 1.5	0.46	5.1 ± 1.8	5.1 ± 1.9	0.92
Uric acid, μmol/L	338 ± 82	325 ± 83	0.17	345 ± 62	345 ± 90	1.00
Creatinine, μmol/L	81 (71 ~ 93)	72 (64 ~ 85)	<0.001	85 (76 ~91)	79 (65 ~ 92)	0.12
Cystatin C, mg/L	1.07 (0.85 ~ 1.14)	0.80 (0.69 ~ 0.90)	< 0.001	1.12 (0.81 ~ 1.24)	0.86 (0.68 ~ 1.12)	0.002
GFR_{MDRD}, mL/min/1.73m^2	86.3 (71.9 ~ 99.5)	100.0 (85.0 ~ 119.1)	< 0.001	83.2 (71.6 ~ 90.7)	95.9 (77.3 ~ 114.9)	0.006
GFR_{EPI}, mL/min/1.73m2	85.8 (71.1 ~ 96.0)	95.0 (83.3 ~ 102.6)	< 0.001	78.7 (68.6 ~ 90.3)	93.0 (76.1 ~ 101.9)	0.004
GFR_{CYS}, mL/min/1.73m^2	68.9 (61.5 ~ 94.4)	101.6 (84.5 ~ 111.2)	< 0.001	58.9 (55.8 ~ 96.6)	97.1 (65.8 ~ 111.1)	< 0.001
Medication, n (%)						
ACE inhibitor/ARB	69 (55.2)	104 (58.8)	0.54	12 (36.4)	40 (42.6)	0.53
β-blocker	54 (42.7)	71 (39.8)	0.59	17 (51.5)	36 (38.3)	0.19
Calcium channel blocker	35 (28.2)	47 (26.7)	0.78	9 (27.3)	17 (18.1)	0.26
Nitrates	74 (59.2)	113 (64.2)	0.41	13 (39.4)	42 (44.7)	0.60
Statins*	69 (55.2)	104 (58.8)	0.54	12 (36.4)	52 (55.3)	0.06
Antidiabetic therapy	98 (78.4)	149 (84.2)	0.20	/	/	/

Data are mean ± SD or median (25th ~ 75th percentiles) or number (%)
ACE, angiotension converting enzyme; ARB, angiotension receptor blocker; GFR, glomerular filtration rate, HbA1c, glycoseylated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein
*Statins: mainly simvastatin, pravastatin and atorvastatin.

Table 1: Baseline characteristics and biochemical assessment in diabetic and non-diabetic patients with poor and good collateralization.

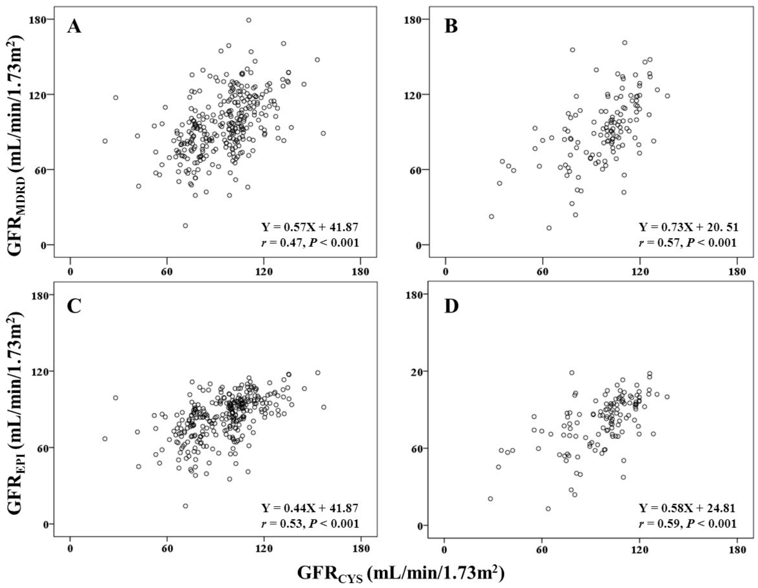

Figure 1: Correlation between glomerular filtration rates estimated with creatinine-based MDRD (GFR_{MDRD}) and CKD-EPI (GFR_{EPI}) equations and cystatin C-based formula (GFR_{CYS}) in diabetic (A,C) and non-diabetic (B,D) patients.

		Diabetes		Non-diabetes	
	Variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Model 1	Gender	2.17 (1.16 ~ 4.09)	0.016	3.70 (1.18 ~ 11.57)	0.024
	Age > 65y	2.30 (1.35 ~ 3.92)	0.002	3.79 (1.39 ~ 10.32)	0.009
	Non-hypertension	2.05 (1.19 ~ 3.54)	0.010	2.89 (1.07 ~ 7.81)	0.037
	Dyslipidemia	1.95 (1.17 ~ 3.25)	0.010	3.09 (1.17 ~ 8.18)	0.023
	Smoke	2.25 (1.27 ~ 3.99)	0.006	1.26 (0.46 ~ 3.47)	0.657
	Multivessel disease	1.57 (0.79 ~ 3.10)	0.197	2.46 (0.58 ~ 10.42)	0.221
	GFR_{MDRD} < 90 mL/min/1.73m^2	2.86 (1.71 ~ 4.79)	< 0.001	3.24 (1.11 ~ 9.49)	0.032
Model 2	Gender	2.05 (1.10 ~ 3.81)	0.024	3.07 (1.01 ~ 9.34)	0.048
	Age > 65y	2.07 (1.20 ~ 3.57)	0.009	3.00 (1.06 ~ 8.52)	0.039
	Non-hypertension	2.03 (1.19 ~ 3.46)	0.010	2.78 (1.04 ~ 7.47)	0.042
	Dyslipidemia	2.04 (1.23 ~ 3.38)	0.006	3.37 (1.28 ~ 8.86)	0.014
	Smoke	2.35 (1.32 ~ 4.18)	0.004	1.03 (0.39 ~ 2.74)	0.953
	Multivessel disease	1.67 (0.86 ~ 3.27)	0.131	2.86 (0.62 ~ 13.14)	0.177
	GFR_{EPI} < 90 mL/min/1.73m^2	2.36 (1.35 ~ 4.14)	0.003	4.50 (1.15 ~ 17.58)	0.031
Model 3	Gender	1.78 (0.92 ~ 3.44)	0.089	3.73 (1.21 ~ 11.5)	0.022
	Age > 65y	1.95 (1.11 ~ 3.42)	0.020	3.88 (1.43 ~ 10.58)	0.008
	Non-hypertension	2.40 (1.34 ~ 4.28)	0.003	2.45 (0.93 ~ 6.47)	0.070
	Dyslipidemia	2.04 (1.19 ~ 3.49)	0.009	4.18 (1.56 ~ 11.16)	0.004
	Smoke	2.47 (1.34 ~ 4.56)	0.004	1.12 (0.42 ~ 3.01)	0.820
	Multivessel disease	1.74 (0.87 ~ 3.51)	0.120	2.58 (0.63 ~ 10.64)	0.190
	GFR_{CYS} < 90 mL/min/1.73m^2	6.21 (3.53 ~ 10.91)	< 0.001	3.30 (1.20 ~ 9.04)	0.020

GFR_{MDRD},GFR_{EPI} and GFR_{CYS} are included in model 1, 2 and 3, respectively.
GFR, glomerular filtration rate

Table 2: Logistic regression analyses for poor collateralzation in diabetic and non-diabetic patients.

the presence of poor collateralization in diabetic patients (Figure 3), along with a NRI of 15.0% (*P*=0.025) and 20.1% (*P*=0.002) and an IDI of 10.4% (*P*<0.001) and 11.8% (*P*<0.001), respectively. While in non-diabetic patients, the area under the curve of GFR_{CYS} was not significantly different from that of GFR_{MRDR} (0.71 vs. 0.66, *P*=0.40) and GFR_{EPI} (0.71 vs. 0.67, *P*=0.48) with lower power of the NRI (-2.0%, *P*=0.89 and -4.0%, *P*=0.75) and IDI (5.1%, *P*<0.001 and 4.3%, *P*<0.001).

Multivariate logistic regression analysis revealed that after adjusting for possible confounding variables, a GFR<90 mL/min/1.73 m^2 estimated with the cystatin C- based formula was more independently associated with poor collateralization (OR: 6.21) compared with that estimated with the MDRD (OR: 2.86) and the CKD-EPI (OR: 2.36) equations in diabetic patients (*P*=0.042 and *P*=0.015). In contrast, $GFR_{CYS,}$ GFR_{MDRD} and GFR_{EPI} were similar for assessing coronary collateralization in non-diabetic patients (OR: 3.30 vs. 3.34 and 4.50, *P*=0.980 and *P*=0.715) (Table 2).

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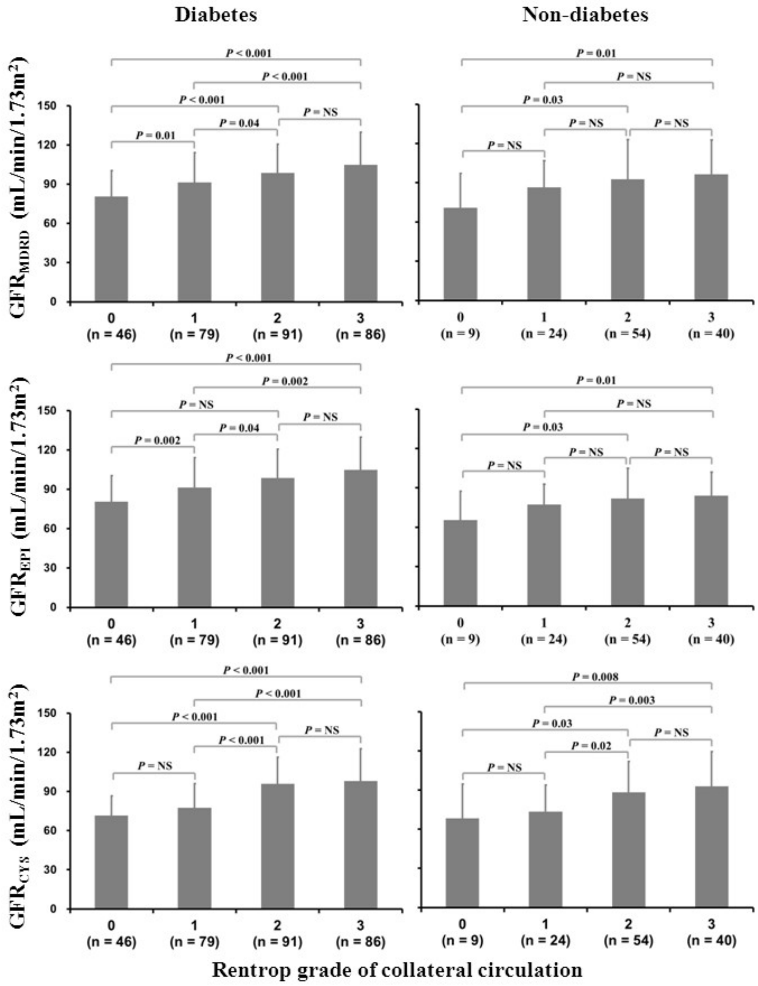
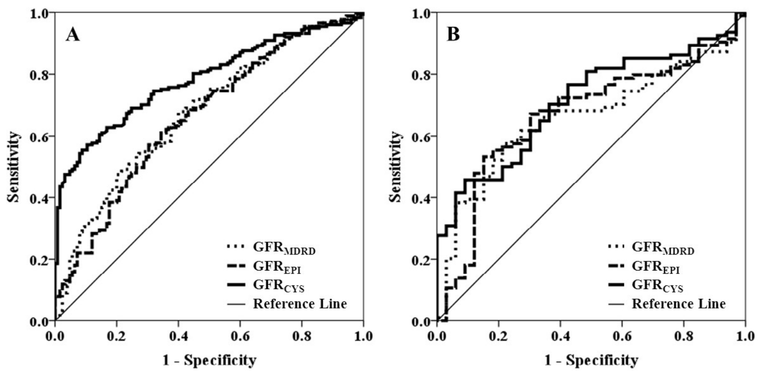


Figure 2: Relationship between GFR estimated with creatinine-based MDRD (GFR_{MDRD}) and CKD-EPI (GFR_{EPI}) equations and cystatin C-based formula (GFR_{CYS}) and Rentrop grade of collateral circulation in diabetic and non-diabetic patients. NS, not significant.



	AUC (95% CI)	*P* value	AUC (95% CI)	*P* value
GFR_{MDRD}	0.68 (0.62 ~ 0.73)	< 0.001	0.66 (0.57 ~ 0.74)	0.006
GFR_{EPI}	0.66 (0.60 ~ 0.73)	< 0.001	0.67 (0.56 ~ 0.77)	0.004
GFR_{CYS}	0.78 (0.73 ~ 0.83)	< 0.001	0.71 (0.62 ~ 0.78)	< 0.001

Figure 3: Receiver operating characteristic (ROC) curve of GFR_{MRDR} (dotted line), GFR_{EPI} (dashed line) and GFR_{CYS} (solid line) for detecting the presence of poor collateralization in diabetic (A) and non-diabetic (B) patients. AUC, area under curve; CI, confidence interval.

Discussion

This study is the first to demonstrate that compared with the creatinine-based MDRD and CKD-EPI equations, the cystatin C-based definition of renal dysfunction has better clinical utility for predicting poor coronary collateralization in type 2 diabetic patients with stable coronary artery disease.

Our results support the view that presence and extent of coronary collateralization were influenced by multiple clinical, biochemical and angiographic factors [5,33], and substantiate a notion that impaired renal function as manifested by reduced GFR was frequently associated with poor collateralization in patients with diabetes. In this study, patients with diabetes developed poor collateralization at lower creatinine and cystatin C levels compared with their non-diabetic counterparts, suggesting that coronary collateral formation is more adversely affected by concomitant renal dysfunction in diabetic patients. It is well recognized that diabetes represents an independent risk factor for poor coronary collateralization. In a diabetic setting, advanced glycation end-products (AGEs) form and interact with receptor for AGEs (RAGE), leading to the development and acceleration of diabetic nephropathy [26,34,35]. Uremic toxins exert a deleterious effect on several components necessary for collateral development, including pro-angiogenic growth factors, endothelial function, redox state of coronary circulation, intracellular signaling, leukocytes and bone marrow-derived progenitor cells [10,36]. Renal dysfunction might further potentiate diabetes through an increase in insulin resistance, further causing poor coronary collateralization [37,38].

Another major finding of this study is that despite a similar pattern of association with coronary collateralization, GFR_{CYS} correlated more closely with Rentrop score than GFR_{MDRD} and GFR_{EPI} in diabetic patients. The agreement of cystatin C- and creatinine- based equations for identifying diabetic patients with at least mild renal dysfunction assessed by Fleiss-Cohen κ coefficients was fair, which is also consistent with a low correlation coefficient of GFRcys with GFR_{MDRD} and GFR_{EPI}. Interestingly, ROC curve analysis, reclassification and discrimination of a cystatin C-based estimating equation and multivariate logistic regression models raised the potential for a better utility compared with creatinine ones in predicting the presence of poor coronary collateralization, particularly for diabetic patients with early changes of kidney function. One of the explanations for that was likely GFR based on serum creatinine level could not accurately estimate kidney function in patients with diabetes [15]. Previous studies have shown that the creatinine-based abbreviated MDRD formula is limited by the influence of a number of non-renal factors, including muscle mass and age of the individual, and often underestimates GFR by approximately 10-40% in the hyper-filtrating range [15,39]. Likewise, this formula is developed from a population of predominantly non-diabetic subjects with decreased GFR. The CKD-EPI equation has been introduced as a better means to estimate GFR in observational research [16], but data from patients with diabetes comparing this creatinine-based equation with the cystatin C-based formula in the evaluation of coronary collateralization are still lacking. Our results show that GFR_{CYS} provides a better accuracy and precision of renal function compared with GFR determined on creatinine levels [21,40]. Cystatin C levels in serum are mainly determined by GFR as this molecule is freely filtered in the glomeruli and almost completely reabsorbed and catabolized by the proximal renal tubular cells [41]. Several investigations have indicated that serum cystatin C was superior, or at least equivalent to serum creatinine as a GFR marker in patients with native kidneys, especially in diabetic patients with mild or moderate renal dysfunction [18-20]. In addition, cystatin C has been shown to inhibit endothelial cell tubule formation and display anti-angiogenic characteristics in vitro [42].

Early detection of poor coronary collateralization may have important clinical relevance as cardiovascular mortality associated with coronary artery disease is significantly higher in patients with diabetes compared with their non-diabetic counterparts, partly because of impaired coronary collateralization [38]. From the results of present study, GFR_{CYS}<90 mL/min/1.73 m^2 reflected a 6-fold increased risk of poor collateralization, and the odds ratio at such a GFR_{CYS} level was significantly higher than that estimated with the creatinine-based MDRD and CKD-EPI equations in diabetic patients. This suggests that cystatin C-based definition of renal dysfunction was not only an ideal marker reflecting early phase of renal impairment, but also has potential advantages to predict poor coronary collateralization in diabetic patients. Since therapeutic induction of collateral growth is an attractive complementary treatment for coronary revascularization, clinical evaluation of coronary collateralization remains desirable before new non-invasive methods are emerging [1,2].

Limitations

We recognize that there are several limitations in our study. First, the study is cross-sectional for the point of coronary collateral investigation, thereby allowing us to detect association, not to predict outcome. Second, we evaluated the presence and degree of collaterals according to the Rentrop scoring system. Coronary collaterals may be more accurately assessed by collateral flow index with simultaneous measurement of aortic pressure and the distal pressure within the occluded segment of the culprit coronary artery [1]. Nevertheless, angiographic assessment of coronary collaterals is easy to incorporate into the routine clinical practice. Third, the study population was unique as all patients had stable angina. Previous studies have shown that sequential episodes of myocardial ischemia are a stimulating factor in the recruitment of collateral vessels [43]. Finally, available data on cystatin C-based GFR equation remain very limited, and further large-scale studies with molecular experiments are required to clarify the mechanisms of renal dysfunction effect on coronary collateralization.

Conclusions

The present study has demonstrated an association between renal dysfunction and reduced coronary collaterals in type 2 diabetic patients with stable angina and chronic total occlusion. Compared with the creatinine-based MDRD and CKD-EPI equations, the cystatin C-based GFR formula has better clinical utility for identifying patients with poor collateralization. These findings may offer a rationale in improving risk assessment and clinical outcomes in this unique high-risk cohort with aggressive intervention of diabetes and nephropathy [20,44,45].

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