



## Clinical and angiographic features associated with coronary collateralization in stable angina patients with chronic total occlusion

Zhen SUN<sup>§1</sup>, Ying SHEN<sup>§1</sup>, Lin LU<sup>1,2</sup>, Rui-yan ZHANG<sup>1</sup>, Li-jin PU<sup>1</sup>, Qi ZHANG<sup>1</sup>,  
Zheng-kun YANG<sup>1</sup>, Jian HU<sup>1</sup>, Qiu-jing CHEN<sup>2</sup>, Wei-feng SHEN<sup>†‡1,2</sup>

(<sup>1</sup>Department of Cardiology, Shanghai Ruijin Hospital, Shanghai 200025, China)

(<sup>2</sup>Institute of Cardiovascular Diseases, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China)

<sup>†</sup>E-mail: rjshenweifeng@gmail.com

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**Abstract:** Objective: Coronary collateral circulation is an alternative source of blood supply to myocardium in the presence of advanced coronary artery disease. We sought to determine which clinical and angiographic variables are associated with collateral development in patients with stable angina and chronic total coronary occlusion. Methods: Demographic variables, biochemical measurements, and angiographic findings were collected from 478 patients with stable angina and chronic total coronary occlusion. The presence and extent of collaterals supplying the distal aspect of a total coronary occlusion from the contra-lateral vessel were graded from 0 to 3 according to the Rentrop scoring system. Results: Low (Rentrop score of 0 or 1) and high (Rentrop score of 2 or 3) coronary collateralizations were detected in 186 and 292 patients, respectively. Despite similar age, cigarette smoking, and medical treatment, patients with low collateralization were female in a higher proportion and less hypertensive, and had higher rates of type 2 diabetes and dyslipidemia than those with high collateralization (for all comparisons,  $P < 0.05$ ). In addition, patients with low collateralization exhibited more single-vessel disease, less right coronary artery occlusion, more impaired renal function, and higher serum levels of high-sensitivity C-reactive protein (hsCRP) compared with those with high collateralization. Multivariate analysis revealed that age of  $\geq 65$  years, female gender, diabetes, no history of hypertension, dyslipidemia, moderate to severe renal dysfunction, single-vessel disease, and elevated hsCRP levels were independently associated with low coronary collateralization. Conclusions: Coronary collateralization was reduced in almost 40% of stable angina patients with chronic total occlusion, which was related to clinical and angiographic factors. The impact of coronary collateralization on outcomes after revascularization needs further investigation.

**Key words:** Stable angina, Coronary collateral circulation, Risk factors, Angiography, Chronic total coronary occlusion  
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### 1 Introduction

In the human heart, the development of coronary collaterals serves as a conduit, bridging significantly stenotic or occluded coronary vessels, and constitutes

a natural bypass system (Seiler, 2010; Traupe *et al.*, 2010). Currently, routine coronary angiography reveals that about 20%–30% of patients with significant coronary artery disease had chronic total occlusion. The number is expected to rise as a result of improved survival of patients with acute coronary syndrome, due to rapid advances in medical and interventional therapy for patients with coronary artery disease. Despite the complete interruption of antegrade blood

<sup>‡</sup> Corresponding author

<sup>§</sup> The two authors contributed equally to this work

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flow caused by heavy atherosclerotic plaque burden or arterial thrombosis, the frequency of myocardial infarction in areas subtended by chronic total occlusion varies considerably (Fefer *et al.*, 2012), and the degree of myocardial injury downstream of epicardial chronic total occlusion is inversely correlated with the degree of angiographic coronary collateral circulation (Choi *et al.*, 2013). Well-developed coronary collaterals have the potential to alleviate myocardial ischemia, preserve residual contractility, reduce cardiovascular events (Regieli *et al.*, 2009; Meier *et al.*, 2012), and even save lives in patients with severe coronary artery occlusion (Meier, 2011). The complex mechanism mediating the development of coronary collateral vessels in the heart is still not well-understood. In fact, the extent of coronary collateralization differs greatly among patients and is affected by multiple clinical, angiographic, and biochemical factors and inflammatory cytokines (Schirmer *et al.*, 2009; Zorkun *et al.*, 2013). Note that the inconclusive roles of age, gender, heart rate, and risk factors for coronary artery disease in the development of coronary collateralization reported previously may be partly due to the heterogeneity of study populations and different clinical conditions. A severe coronary artery obstruction is a well-known prerequisite for spontaneous collateral recruitment (Levin, 1974) and various clinical manifestations of coronary artery disease influence collateral formation (Hsu *et al.*, 2012; Rocic, 2012).

Because of the apparent prognostic implications of coronary collateralization, a better understanding of the factors influencing the development of coronary collaterals is essential. Therefore, in this study we sought to determine the clinical and angiographic features associated with coronary collateralization in patients with stable angina and chronic total coronary occlusion.

## 2 Materials and methods

### 2.1 Study population

Between January 2008 and March 2013, a total of 612 consecutive patients with stable angina and chronic total occlusion (>3 months) of at least one major epicardial coronary artery were screened, from the database of Shanghai Ruijin Hospital Percutane-

ous Coronary Intervention (PCI) Outcomes Program. This program utilizes clinical and angiographic information to estimate risk-adjusted outcomes. Stable angina was diagnosed according to the criteria recommended by the American College of Cardiology/American Heart Association (Fraker *et al.*, 2007). 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 (Wang *et al.*, 2013). For the purpose of this study and to avoid confounding data, patients who had a history of coronary artery bypass grafting ( $n=49$ ) or who had received PCI within the prior three months ( $n=54$ ) were excluded. Patients with type 1 diabetes, identified by measurement of C-peptide levels, were excluded ( $n=8$ ). We also excluded those with heart failure, pulmonary heart disease, malignant tumor, or immune system disorders ( $n=23$ ). The remaining 478 eligible patients with stable angina and chronic total occlusions (363 men and 115 women, mean age ( $65\pm 10$ ) years) were enrolled in this study.

### 2.2 Clinical parameters and biochemical measurement

Demographic variables, risk factors for coronary artery disease, lipid profile, renal function, and medical treatment were recorded. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg. The diagnosis of type 2 diabetes mellitus was made according to the criteria of the American Diabetes Association, and included symptoms of diabetes plus a casual plasma glucose concentration beyond 200 mg/dl (11.1 mmol/L), or an increased fasting glucose level (126 mg/dl (7.0 mmol/L)) or 2-h postprandial glucose level (200 mg/dl (11.1 mmol/L)) during an oral glucose tolerance test. Hyperlipidemia was diagnosed according to the guidelines of the National Cholesterol Education Program (ATP III). The abbreviated modification of diet in renal disease (MDRD) equation was used to estimate the glomerular filtration rate (eGFR):  $eGFR=186(c/88.4)-1.154A-0.203b$ , where  $c$  is the concentration of creatinine,  $A$  is age, and  $b$  is the constant, which equals to 0.742 for female. At least moderate renal dysfunction was defined as eGFR  $< 60$  ml/(min $\cdot 1.73$  m $^2$ ). Serum levels of high-sensitivity

C-reactive protein (hsCRP) were measured using an enzyme-linked immunosorbent assay (ELISA) kit.

### 2.3 Coronary angiography and collateral scoring

Coronary angiography was performed through the femoral or radial approach (Pu *et al.*, 2012; Shen *et al.*, 2012). Intracoronary administration of nitroglycerin was encouraged prior to angiography. Coronary angiograms were reviewed by two experienced cardiologists who were blind to the study protocol and biochemical measurements. Any difference in interpretation was resolved by a third reviewer who was blind to the readings of the first two reviewers.

Significant coronary artery disease was diagnosed if there was  $\geq 70\%$  diameter stenosis in at least one major epicardial coronary artery. Left main coronary artery narrowing of  $\geq 50\%$  was considered as 2-vessel disease. The severity of coronary artery disease was determined by the number of significantly diseased coronary arteries. Multi-vessel coronary disease was defined as the presence of  $\geq 70\%$  luminal diameter stenosis involving at least two major epicardial coronary arteries. The recorded data also included the vessel to which the collaterals were connected and the grade of coronary collateral circulation.

The presence and extent 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 (Rentrop *et al.*, 1985): 0, 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 having low (Rentrop score of 0 and 1) or high (Rentrop score of 2 and 3) coronary collateralization. In patients with more than one total coronary occlusion, the vessel with the highest collateral grade was chosen for analysis.

### 2.4 Statistical analysis

Continuous variables are presented as mean  $\pm$  standard deviation (SD) and categorical data are summarized as frequencies or percentages. The differences between groups were analyzed by Chi-square test for categorical clinical variables and by Student's unpaired *t*-test for continuous variables. Subsequently,

significantly correlated variables in the univariate analysis or relevant variables were further analyzed by logistic or multiple regression analysis. All *P*-values were 2-sided with a significance level of  $P < 0.05$ . The Statistical Package for the Social Sciences (SPSS) 11.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

## 3 Results

### 3.1 Clinical and angiographic characteristics

Of the total 478 patients, 75.9% were men, 38.1% currently smoked cigarettes, 33.1% had type 2 diabetes, 67.8% suffered hypertension, and 45.8% had hyperlipidemia. Moderate to severe renal dysfunction occurred in 17.6% of the population, and 77.2% of patients had multi-vessel coronary disease.

Low (Rentrop score of 0 or 1) and high (Rentrop score of 2 or 3) coronary collateralization was detected in 186 and 292 patients, respectively. Despite similar age, cigarette smoking, and medical treatment, patients with low collateralization were female in a higher proportion and less hypertensive, and had higher rates of type 2 diabetes and dyslipidemia before statin medications than those with high collateralization (for all comparisons,  $P < 0.05$ ). In addition, patients with low collateralization exhibited more single-vessel coronary artery disease, less right coronary artery occlusion, more impaired renal function, and higher serum levels of hsCRP compared with those with high collateralization ( $P < 0.05$ ) (Table 1).

### 3.2 Binary logistic regression analysis

Variables that presented a level of statistical significance of  $< 0.20$  in the univariate analyses (Table 1) were chosen for multivariate logistic regression analysis to determine independent risk factors for low coronary collateralization. We found that age of  $\geq 65$  years, female gender, diabetes, no history of hypertension, hyperlipidemia, moderate to severe renal dysfunction, and single-vessel coronary disease were independently associated with low coronary collateralization (Table 2).

The data were then dichotomized according to the age, gender, presence or absence of hypertension, hyperlipidemia, diabetes, renal dysfunction, and the

number of significant diseased coronary arteries. We found that the rate of low collateralization was significantly higher in patients older than 65 years or female with no prior hypertension, but who had hyperlipidemia, diabetes, at least moderate renal insufficiency, and single-vessel disease (all  $P<0.05$ ) (Fig. 1).

#### 4 Discussion

It is well known that the development of coronary collateral circulation is influenced by multiple clinical, biochemical, and angiographic factors. In this unique cohort of stable angina patients with chronic total coronary occlusion, we have shown that

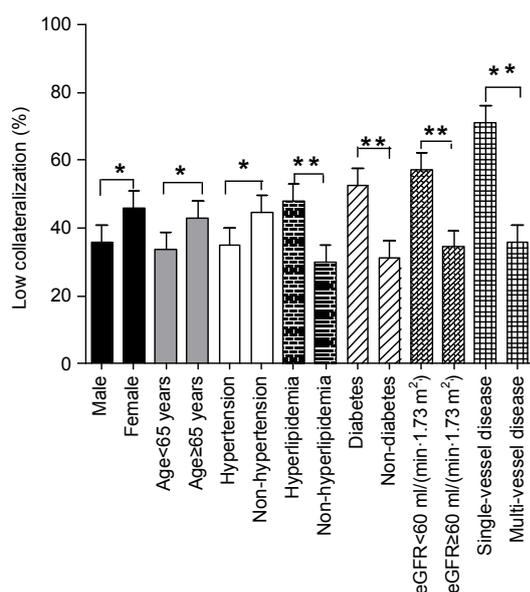
**Table 1** Baseline characteristics of patients with low or high coronary collateralization

Parameter	Low collateralization group (n=186)	High collateralization group (n=292)	P value
Age (year)	66±10	64±11	0.07
Age ≥65 years	102 (55.7%)	136 (46.1%)	0.04
Male	130 (71%)	233 (79%)	0.048
Cardiovascular risk factors			
Smoking	69 (37.1%)	113 (38.3%)	0.72
Hypertension	115 (61.8%)	209 (71.6%)	0.026
Hyperlipidemia	107 (57.5%)	112 (38.4%)	<0.001
Diabetes mellitus	83 (45.4%)	75 (25.4%)	<0.001
Systolic blood pressure (mmHg)	136±17	140±16	0.008
Diastolic blood pressure (mmHg)	82±10	85±8	0.001
Triglyceride (mmol/L)	1.91±1.19	1.79±0.99	0.06
Total cholesterol (mmol/L)	4.37±1.43	4.14±1.12	0.05
HDL-C (mmol/L)	0.98±0.25	1.05±0.26	0.02
LDL-C (mmol/L)	2.69±1.40	2.57±0.89	0.20
Apoprotein-A (g/L)	1.22±0.25	1.19±0.23	0.45
Apoprotein-B (g/L)	1.00±0.33	0.88±0.27	0.009
Lipoprotein (a) (g/L)	0.24±0.19	0.24±0.21	0.57
Fasting glucose (mmol/L)	6.02±1.97	5.39±1.39	<0.001
HbA1c (%)	6.44±1.10	6.19±1.11	<0.001
BUN (mmol/L)	5.50±1.95	5.07±1.65	0.001
Creatinin (μmol/L)	82.8±19.8	80.8±27.3	0.003
Uric acid (μmol/L)	339±80	328±79	0.15
eGFR<60 ml/(min·1.73 m <sup>2</sup> )	48 (26.2%)	36 (12.2%)	<0.001
High-sensitivity CRP (mg/L)	5.85±3.01	5.28±2.71	0.03
Medications			
Oral antiplatelet	168 (100%)	292 (100%)	1.00
ACEI	79 (42.5%)	138 (47.3%)	0.30
β-blockers	86 (46.2%)	121 (41.4%)	0.31
Nitrates	48 (25.8%)	72 (25.7%)	0.77
Calcium antagonists	23 (28.4%)	15 (25.0%)	0.653
Statins	175 (94.1%)	285 (97.6%)	0.89
Number of significant CAD			
1-vessel disease	51 (27.9%)	58 (19.7%)	0.004
2-vessel disease	53 (29.0%)	129 (43.7%)	
3-vessel disease	79 (43.2%)	108 (36.6%)	

Values are expressed as mean±SD or number of patients (percentage). Chi-square for categorical variables. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; ACEI: angiotensin-converting enzyme inhibitor; CAD: coronary artery disease

**Table 2 Multivariable analysis of risks of low collateralization in patients with chronic total occlusion**

Variable	OR	95% CI	P value
Female	1.770	1.022–3.329	0.049
Age $\geq 65$ years	1.556	1.002–2.369	0.039
Hypertension	0.524	0.336–0.818	0.004
Hyperlipidemia	2.168	1.426–3.296	<0.001
Diabetes mellitus	2.567	1.650–3.995	<0.001
eGFR<60 ml/(min $\cdot$ 1.73 m $^2$ )	3.069	1.761–5.350	<0.001
Single-vessel disease	1.902	1.155–3.302	0.011



**Fig. 1 Occurrence of low coronary collateralization in patients with various clinical and angiographic features**  
The significance of differences is indicated by \*  $P < 0.05$  or \*\*  $P < 0.01$

old age, female gender, no prior hypertension, presence of diabetes, hyperlipidemia, at least moderate renal dysfunction, and single-vessel coronary disease were independently associated with low coronary collateralization.

#### 4.1 Traditional risk factors

Consistent with previous angiographic studies (Boodhwani *et al.*, 2006; Wang *et al.*, 2013; van der Hoeven *et al.*, 2013), our results indicated that coronary collateral development was lower in females and declined with increasing age of the patients. In contrast, well-developed collaterals were more frequently detected in hypertensive patients than in their non-hypertensive counterparts. Clearly, high blood pressure (especially elevated diastolic blood pressure) provides an increased gradient between central aortic pressure and left ventricular end-diastolic pressure,

which is one of the main prerequisites for coronary collateral formation. Recently, Wang *et al.* (2013) found that elevated diastolic blood pressure is related to high coronary collateralization by altering blood flow velocity in diastole and tangential fluid shear stress on the endothelial surface. Differences in coronary collateral growth may be one of the pathophysiological mechanisms responsible for the J-curve phenomenon in the relationship between diastolic blood pressure and cardiovascular risk. In experimental animal studies, hyperlipidemia, particularly hypercholesterolemia, was shown to be an inhibitor of arteriogenesis (Lin *et al.*, 2010). However, data on the relationship between coronary collateral formation and hyperlipidemia remain controversial, partly because of the use of different techniques for grading the collateral flow (van der Hoeven *et al.*, 2013).

In this study, we observed that diabetes correlated negatively with the development of collaterals and was also an independent predictor of poorly developed collateral circulation. Kilian *et al.* (2002) found that even in patients with pre-diabetes, the fasting glucose level was an independent predictor of coronary collateral formation. The mechanism by which diabetes induces poor collateral growth is complex and remains unclear. In vitro and animal experiments have shown that high glucose levels can cause endothelial dysfunction (Williamson *et al.*, 1990), and endothelial cell function is vital for coronary collateral formation. Hyperglycemia reduced coronary collateral blood flow through a nitric oxide-mediated mechanism in a dog model (Kersten *et al.*, 2001). In diabetic patients, increased levels of endostatin and angiostatin are negatively correlated with coronary collateral formation (Kadi *et al.*, 2011).

#### 4.2 Renal dysfunction

So far, data regarding the prediction of low collateralization in chronic renal dysfunction patients with stable coronary artery disease remain scant (Hsu *et al.*, 2012). In this study, a high percentage of patients with at least moderate renal dysfunction had poor coronary collateralization. Xie *et al.* (2011) reported that coronary collateral formation is significantly reduced in stable coronary artery disease patients with mild to moderate renal insufficiency (eGFR < 80 ml/(min $\cdot$ 1.73 m $^2$ )). Recently, Duran *et al.* (2013) hypothesized that an association between mild

to moderate renal impairment and the presence of coronary collateral vessels may be explained by increased ischemia and the extent and severity of coronary artery disease. In patients with chronic renal dysfunction, hypoxia in the kidney induces the expression of proteins, such as the hypoxia-inducible factor and vascular endothelial growth factor, which are involved in angiogenesis and are associated with coronary collateral development.

We postulated that there was a synergistic effect of hypertension and diabetes on low coronary collateralization. Blood pressure is usually elevated in patients with renal dysfunction as a result of fluid retention and over-production of vasoactive hormones via the rennin-angiotensin system. These changes may aggravate hypertension. Diabetes is also an important cause of chronic renal insufficiency. Thus, chronic renal dysfunction may further potentiate hypertension and diabetes and cause low coronary collateralization.

#### 4.3 Coronary disease severity and occluded vessels

Numerous studies have demonstrated that coronary collateral formation is dependent mainly on the severity of coronary artery disease, with high collateralization in patients with extensive coronary lesions. In line with previous findings, our present study showed that the number of significantly diseased coronary arteries was associated with high collateralization not only in univariate analysis but also in multivariate analysis. Hence, the extent of coronary atherosclerosis plays an important role in coronary collateral formation for stable angina patients with chronic total occlusion.

Coronary collaterals were significantly better developed in patients with right coronary artery occlusion, which is consistent with previous findings (Elsman *et al.*, 2004). This may imply better collateralization from the left coronary artery (especially the left anterior descending artery) than from other vessels, possibly due to the larger size of the artery.

#### 4.4 Inflammatory cytokines

Inflammation has emerged as being central to the initiation and progression of atherosclerosis, and a complex interaction exists between new blood vessel formation and inflammation (Imhof and Aurrand-Lions, 2006). In the present study, an increased

hsCRP level in serum was detected in patients with low collateralization. This is consistent with previous reports and supports a notion that a graded inverse independent association exists between CRP levels and collateral development in patients with stable angina pectoris (Kerner *et al.*, 2007). Seiler (2010) demonstrated that tumor necrosis factor- $\alpha$  was detectable more often in patients with insufficient coronary collateral. Guray *et al.* (2004) reported an association between poor collateral circulation and an elevated concentration of soluble adhesion molecules, a marker of cytokine-induced endothelial activation.

#### 4.5 Study limitations

We recognize several limitations in our study. First, this study was cross-sectional, thereby allowing us to detect associations, but not to formulate predictions. Likewise, the potential mechanisms were not fully elucidated. Second, coronary collateralization was assessed by angiographic images. Measuring the collateral flow index using the intravascular Doppler technique may provide a more objective physiological assessment of collateral grade.

### 5 Conclusions

Our data revealed that almost 40% of stable angina patients with chronic total occlusion had low coronary collateralization. Old age, female gender, no prior hypertension, hyperlipidemia, diabetes, at least moderate renal dysfunction, and less severe coronary artery disease were associated with low collateralization and may have a negative synergistic effect on collateral development. These findings provide new insights for risk stratification and medical and revascularization treatments in patients with coronary artery disease.

#### Compliance with ethics guidelines

Zhen SUN, Ying SHEN, Lin LU, Rui-yan ZHANG, Li-jin PU, Qi ZHANG, Zheng-kun YANG, Jian HU, Qiu-jing CHEN, and Wei-feng SHEN declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on

human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study.

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### **Recommended paper related to this topic**

#### **Screening for significant atherosclerotic renal artery stenosis with a regression model in patients undergoing transradial coronary angiography/intervention**

Authors: Li-jin PU, Ying SHEN, Rui-yan ZHANG, Qi ZHANG, Lin LU, Feng-hua DING, Jian HU, Zheng-kun YANG, Wei-feng SHEN

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**Abstract:** Objective: Early detection of atherosclerotic renal artery stenosis (ARAS) is clinically important with respect to blood pressure control, prevention of renal insufficiency, and even improving survival. We investigated whether the presence of significant ARAS (luminal diameter narrowing  $\geq 70\%$ ) could be predicted using a logistic regression model before coronary angiography/intervention. Methods: Initially, we developed a logistic regression model for detecting significant ARAS based upon clinical and angiographic features and biochemical measurements in a cohort of 1813 patients undergoing transfemoral coronary and renal angiography. This model was then prospectively applied to an additional 495 patients who received transradial renal angiography to ascertain its predictive accuracy for the presence of significant ARAS. Results: Multivariate regression analysis revealed that older age ( $\geq 65$  years), resistant hypertension, type 2 diabetes, creatinine clearance (Ccr)  $\leq 60$  ml/min, and multivessel coronary disease were independent predictors for significant ARAS. A logistic regression model for detecting ARAS by incorporating conventional risk factors and multivessel coronary disease was generated as:  $P/(1-P) = \exp(-2.618 + 1.112[\text{age} \geq 65 \text{ years}] + 1.891[\text{resistant hypertension}] + 0.453[\text{type 2 diabetes}] + 0.587[\text{Ccr} \leq 60 \text{ ml/min}] + 2.254[\text{multivessel coronary disease}])$ . When this regression model was prospectively applied to the additional 495 patients undergoing transradial coronary and renal angiography, significant ARAS could be detected with a sensitivity of 81.2%, specificity of 88.9%, and positive and negative predictive accuracies of 53.8% and 96.7%, respectively. Conclusions: The logistic regression model generated in this study may be useful for screening for significant ARAS in patients undergoing transradial coronary angiography/intervention.