Int J Clin Exp Med 2016;9(2):4273-4281
www.ijcem.com /ISSN:1940-5901/IJCEM0015503

Original Article

Relationship between the characteristics of the coronary artery stenosis and the cardiovascular risk factors in a large cohort of Chinese catheterized patients

Gao-Liang Yan, Wen-Jie Kong, Dong Wang, Yong Qiao, Xiang Sha, Tian-Yu Cheng, Hai-Rong Zhang, Jian-Tong Hou, Cheng-Chun Tang, Gen-Shan Ma

Department of Cardiology, Zhongda Hospital of Southeast University Medical School, Nanjing 210009, China

Received September 2, 2015; Accepted December 5, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Background: Coronary artery disease (CAD) remains a leading cause of morbidity and mortality in many countries over the world despite major advances in its diagnosis and treatment. Advancing age, male gender, smoking, hypertension, lipid abnormalities, diabetes, positive family history for premature CAD and obesity are classic established risk factors that tend to cluster and interact multiplicatively in promoting CAD. However, the risk of CAD is not uniform among different populations. Ethnic differences as well as socioeconomic, environmental and genetic factors play a determining role in the development of cardiovascular diseases. In the present study, our aim was to examine the prevalence of several CAD risk factors in a group of Chinese Catheterized patients and to evaluate their role as predictors of the disease, the relationship between the characteristics of the coronary artery stenosis and CAD risk factors. Methods: 7968 consecutive patients underwent coronary angiography for suspected CAD during Jan 2000 to Dec 2014 from the department of Cardiology in Zhongda Hospital of Southeast University Medical School. CAD severity was assessed by the calculated Gensini cumulative scores and the number of major coronary arteries (0-3) with ≥50% stenosis in the angiography, Results: Age, male, systolic blood pressure, smoking, hypertension, diabetes mellitus, dyslipidemia, cerebrovascular disease, fasting plasma glucose, Creatinine, total cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol were significantly higher in CAD group than those in Non-CAD patients. Total bilirubin, direct bilirubin, were significantly lower in CAD group than those in Non-CAD patients. However, there were no difference in body mass index, diastolic blood pressure, Family history of CAD, and obesity between both groups. Conclusions: we conclude that age, male gender, hypertension, DM and CKD are independent risk factor of CAD, however, total bilirubin is an independent protective factor for CAD in this cohort of Chinese catheterized patients.

Keywords: Cardiovascular risk factors, coronary artery disease, angiographic severity, stenosis

Introduction

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality in the world [1-3]. Advancing age, male gender, smoking, hypertension, lipid abnormalities, diabetes, positive family history for premature CAD and obesity are classic established risk factors that tend to cluster and interact multiplicatively in promoting CAD. Other risk factors implicated in the etiology of CAD include homocysteine, C-reactive protein, lipoprotein (a), hyperuricemia, high level of Creatinine, and so on [4]. However, the risk of CAD is not uniform among different populations. Ethnic differences as well as socioeconomic, environmental and genetic factors play a determining role in the development of cardiovascular diseases. There is a great interest for unraveling the exact interrelation between clinical and angiographic features in large population of individuals consecutively referred for diagnostic coronary catheterization among Chinese hospitalized patients. Because the angiographic profile of a catheterized patient (stenosis and number of vessels diseased) carries substantial prognostic information for their cardiovascular outcome, determining the exact relationship between clinical and

angiographic characteristics in large representative population is expected to contribute significantly to more effective preventive strategies, by tailoring and individualizing our current approach of risk factor modification.

In the present study, our principal aim was to explore the relationship between established CVD risk factors and specific distribution patterns of coronary atherosclerotic changes (stenosis and number of vessels affected). The secondary goal was to report the prevalence of major risk factors in a large unselected cohort of patients undergoing coronary angiography and, additionally, to evaluate their role as predictors and severity determinants of angiographic CAD.

Methods

Study population

This study included 7968 consecutive suspected CAD patients who firstly underwent cardiac catheterization to evaluation of their typical or atypical clinical symptoms during Jan 2000 to Dec 2014 from the department of cardiology in Zhongda Hospital of Southeast University Medical School. Exclusion criteria were: acute ST-elevated myocardial infarction, previous myocardial infarction history, previous coronary artery bypass surgery or angioplasty. Before angiography, valid weight and height measurements were performed and a detailed clinical, biochemical information was obtained for every patient. Blood samples for measurements of biochemical assessments were immediately obtained intravenously after hospitalization, the default biochemical characteristics contained total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, total bilirubin (TBIL), direct bilirubin (DBIL), Creatinine, serum uric acid, fasting plasma glucose (FPG). Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Southeast University (Nanjing, China); all patients provided written informed consent prior to participation in the current study. The study complied with the Declaration of Helsinki.

Patients whose mean blood pressure levels in the rest were greater or equal to 140/90 mmHg or reported taking antihypertensive medications were classified as hypertension. Dyslipidemia was defined as total cholesterol levels greater than 5.2 mmol/L and/or LDL-C levels greater than 3.4 mmol/L and/or HDL-C levels below 1.04 mmol/L or use of lipid-lowering drugs. The diagnosis of diabetes mellitus (DM) was established when the FPG levels were higher than 7.0 mmol/L on two occasions or if previously diagnosed according to WHO criteria or the patient reported receiving hypoglycemic treatment. The family history for premature coronary heart disease was regarded positive, when the patient reported having a male first-degree relative with an acute coronary event before the age of 55 years or a female first-degree relative with a coronary manifestation before the age of 65. Body mass index (BMI) was calculated for all patients as weight in kilograms divided by the height in meter square, patient who had a BMI of greater or equal to 28 was obesity. Those participants smoking continuous or cumulative at least 100 cigarettes were defined as current smokers and/or smoking continuous or cumulative at least 6 months.

Definitions

The Gensini score [5] was calculated for each patient from the coronary arteriogram. The Gensini score was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and by its geographic importance. Reduction in the lumen diameter and the radiologic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given Gensini scores of 1, 2, 4, 8, 16 and 32, respectively). This score is then multiplied by a factor that takes into account the importance of the lesion's position in the coronary arterial tree, for example, 5 for the left main coronary artery; 2.5 for the proximal left anterior descending coronary artery and proximal left circumflex coronary artery (3.5 if left circumflex coronary artery is dominant); 1.5 for the mid region of the left anterior descending coronary artery; 1 for the distal left anterior descending coronary artery, the first diagonal, the proximal, mid region, and distal regions of the right coronary artery; the posterodescending, the mid region, and distal region of the left circumflex coronary artery (2 for both of them if left circumflex coronary artery is dominant) and the optus margin; and 0.5 for the second diagonal and the posterolateral branch. The Gensini

Table 1. Clinical Characteristics of the Participants (n=7968)

	CAD (n=5364)	Non-CAD (n=2604)	*P* value
Age (years)	60.8±10.4	55.2±10.6	0.000
Male gender (%)	69.6	54.0	0.000
Smoking (%)	46.1	32.8	0.000
Family history of CAD (%)	3.0	3.4	0.335
Hypertension (%)	66.0	50.8	0.000
Dyslipidemia (%)	38.5	30.5	0.000
Diabetic mellitus (%)	22.7	10.2	0.000
CVD (%)	8.2	4.7	0.000
Obesity (%)	19.2	17.6	0.231
SBP (mmHg)	134.6±19.7	129.9±18.8	00000
DBP (mmHg)	80.1±11.5	80.2±11.3	0.694
CR (μmol/L)	83.5±24.2	76.7±19.8	0.000
Uric acid (μmol/L)	351.6±93.9	342.4±87.4	0.007
Triglyceride (mmol/L)	1.9±1.3	1.8±1.4	0.384
Total cholesterol (mmol/L)	4.7±1.1	4.6±1.0	0.003
LDL-C (mmol/L)	2.8±0.9	2.7±0.8	0.000
TBIL (μmol/L)	12.2±6.4	13.7±6.5	0.000
DBIL (μmol/L)	2.9±2.3	3.4±2.3	0.000
FPG (mmol/L)	5.8±1.9	5.4±1.5	0.000

Abbreviations: CAD, coronary artery disease; CVD, cerebrovascular disease; SBP, Systolic blood pressure; DBP, diastolic blood pressure; CR, Creatinine; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TBIL, total bilirubin; FPG, fasting plasma glucose.

score was expressed as the sum of the scores for the all the coronary arteries.

CAD was defined as angiographic atherosclerotic involvement of more than 50% in at least 1 major coronary artery or its major branches. Patients were then divided into CAD and non-CAD (control) groups according to their catheterization results.

The severity of CAD was assessed by the number of arteries (0, 1, 2 or 3) with more than 50% reduction of the luminal diameter of the major coronary arteries in the angiography (if left main coronary artery was involved, defined as left circumflex and left anterior descending). The number of affected vessels (0, 1, 2 or 3) was recorded and confirmed by two independent cardiologists.

Statistical analysis

Continuous quantitative variables were expressed as mean ± standard deviation (SD). Categorical variables were compared using chi-square test. For continuous variables, the difference between 2 groups was assessed using an unpaired t test. Differences between the 4 angiographic affected vessels groups of patients were compared by one-way analysis of variance (ANOVA). Bonferroni correction was used to control the inflation of type I error due to multiple comparisons. Categorical variables were presented as absolute and relative frequencies and the significance of difference between percentages in the 4 groups was evaluated with the chi-square test. Univariate and multivariate binary logistic regression analysis were done to identify the association of the studied variables with CAD. Risk factors independently related to the presence of the number of affected vessels were established through multivariable ordinal logistic regression analysis. The multivariate model included all variables associated with the binary parameter with a *p* value of less than 0.05 by univariate logistic regression analysis. The result was established with the adjusted odds ratio (OR), the confidence interval of the value (95%) and its statistical significance. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 15.0 and all tests were conducted at the 2-tailed 5% level of significance.

Results

Clinical features of the study population

A total of 5140 male and 2828 female patients were angiographically evaluated for clinically suspected CAD. The mean age of the whole population was 59 years (59.0±10.8 years). In all, 5364 consecutive patients (60.8±10.4 years) with angiographically proven CAD and 2604 consecutive individuals (55.2±10.6 years) belonged to control group were included in the study. There were significant differences between the CAD patients and controls regarding risk factors, such as age, male, systolic blood pressure (SBP), smoking, hypertension,

Table 2. Risk Factors and Angiographic Severity of Gensini Scores quartiles

Risk factors	Gensini scores quartiles				*P* value
	Group A	Group B	Group C	Group D	
Age (years)	54.2±10.6	58.6±10.2	60.7±10.4	62.0±10.3	0.000
Male gender (%)	53.3	60.1	69.0	74.2	0.000
Smoking (%)	33.3	38.0	46.0	48.8	0.000
Family history of CAD (%)	3.6	2.6	3.5	2.8	0.319
Hypertension (%)	47.2	61.4	65.2	69.1	0.000
Dyslipidemia (%)	30.8	32.2	38.3	41.7	0.000
Diabetic mellitus (%)	9.6	15.0	21.2	27.5	0.000
CVD (%)	3.8	5.5	8.3	10.3	0.000
Obesity (%)	18.7	19.7	17.1	17.4	0.399
SBP (mmHg)	128.3±18.2	133.7±19.1	134.5±19.9	135.5±20.0	0.000
DBP (mmHg)	79.7±11.1	80.8±11.3	80.4±11.8	79.6±11.4	0.313
CR (μmol/L)	76.5±20.2	79.2±21.3	82.7±22.4	86.1±26.5	0.000
Uric acid (μmol/L)	340.0±86.6	348.0±88.0	350.7±93.5	354.4±96.9	0.009
Triglyceride (mmol/L)	1.8±1.3	1.9±1.5	1.8±1.2	1.9±1.3	0.231
TC (mmol/L)	4.6±1.0	4.7±1.0	4.7±1.1	4.8±1.2	0.000
HDL-C (mmol/L)	1.2±0.3	1.3±0.5	1.2±0.5	1.2±0.5	0.114
LDL-C (mmol/L)	2.6±0.7	2.7±0.8	2.7±0.8	2.9±0.9	0.000
TBIL (μmol/L)	13.8±6.3	12.8±6.9	12.2±6.3	12.2±6.2	0.000
DBIL (μmol/L)	3.3±2.2	3.3±2.9	2.9±2.1	2.9±2.1	0.000
FPG (mmol/L)	5.4±1.5	5.6±1.7	5.7±1.8	6.1±2.1	0.000

Abbreviations: CAD, coronary artery disease; CVD, cerebrovascular disease; SBP, Systolic blood pressure; DBP, diastolic blood pressure; CR, Creatinine; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TBIL, total bilirubin; FPG, fasting plasma glucose.

DM, dyslipidemia, cerebrovascular disease (CVD), FPG, total cholesterol, LDL-C, Creatinine (CR), were significantly higher in CAD group than those in Non-CAD patients (P<0.05). TBIL, DBIL, were significantly lower in CAD group than those in Non-CAD patients (P<0.05). However, there were no difference in diastolic blood pressure (DBP), family CAD history, and obesity between both groups (P>0.05). Frequencies of risk factors of the groups are compared in **Table 1**.

Risk factors and the severity of coronary artery stenosis

The Gensini scores were between 0 to 296 points of all patients, then patients were divided into 4 groups according to the Gensini scores quartiles (0-2, 2-12, 12-40, 40-). It was found that highly gensini scores group were older, and had higher prevalence of male, smoking, hypertension, dyslipidemia, DM, and CVD, higher levels of SBP, Creatinine, total cholesterol, LDL-C, FPG, and lower levels of TBIL, DBIL. However, there were no differences in family CAD history, obesity and levels of DBP, triglycerides, HDL-C between 4 groups. The precise data are given in detail in **Table 2**.

Among the total angiographically patients for CAD, the 0-vessel disease (non-CAD) group comprised 2604(32.7%) patients, the 1-vessel disease group comprised 2303 (28.9%) patients, the 2-vessel disease group comprised 1500 (18.8%) patients, and the 3-vessel disease group comprised 1561 (19.6%) patients. As CAD was angiographically becoming more diffuse and extensive (progressive transition from 0 to 3-vessel disease), advanced age, male gender, smoking, hypertension, dyslipidemia, DM, and CVD, became increasingly prevalent. Meanwhile, the levels of SBP, Creatinine, uric acid, total cholesterol, LDL-C, and FPG became higher. However, the levels of TBIL and DBIL became lower. In contrast, a family CAD history, obesity and levels of DBP, triglycerides and HDL-C did not prove to be significantly associated with the angiographically assessed

Table 3. Risk Factors and Angiographic Severity of CAD (Number of Vessel ≥50% Stenosis)

Risk factors	Number of vessel ≥50% stenosis				*P* value
	0-vessel	1-vessel	2-vessel	3-vessel	
Age (years)	55.2±10.6	58.6±10.4	61.6±10.2	63.4±9.9	0.000
Male gender (%)	54.0	66.6	69.6	74.1	0.000
Smoking (%)	32.8	43.3	46.1	50.3	0.000
Family history of CAD (%)	3.4	2.7	3.2	3.1	0.638
Hypertension (%)	50.8	59.2	70.6	71.5	0.000
Dyslipidemia (%)	30.5	34.7	38.9	43.8	0.000
Diabetic mellitus (%)	1.2	16.2	25.8	29.2	0.000
CVD (%)	4.7	4.9	9.8	11.4	0.000
Obesity (%)	19.2	17.2	17.2	18.5	0.537
SBP (mmHg)	129.9±18.8	133.0±19.2	135.7±20.0	135.8±20.1	0.000
DBP (mmHg)	80.2±11.3	80.3±11.6	80.4±11.7	79.4±11.3	0. 591
CR (μmol/L)	76.7±19.8	80.7±21.0	85.0±26.6	86.1±25.7	0.000
Uric acid (μmol/L)	342.4±87.4	346.7±91.1	353.0±91.1	356.6±99.5	0.003
Triglyceride (mmol/L)	1.8±1.4	1.8±1.3	1.9±1.3	1.9±1.3	0.587
TC (mmol/L)	4.6±1.0	4.7±1.0	4.8±1.2	4.8±1.1	0.000
HDL-C (mmol/L)	1.2±0.3	1.3±0.5	1.2±0.5	1.2±0.5	0.304
LDL-C (mmol/L)	2.7±0.7	2.7±0.8	2.8±0.9	2.9±0.9	0.000
TBIL (μmol/L)	13.7±6.5	12.4±6.3	12.1±6.4	12.1±6.3	0.000
DBIL (μmol/L)	3.4±2.3	3.0±2.6	2.9±2.1	2.8±2.1	0.000
FPG (mmol/L)	5.3±1.5	5.7±1.7	5.9±1.9	6.1±2.2	0.000

Abbreviations: CAD, coronary artery disease; CVD, cerebrovascular disease; SBP, Systolic blood pressure; DBP, diastolic blood pressure; CR, Creatinine; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TBIL, total bilirubin; FPG, fasting plasma glucose.

severity of coronary. **Table 3** shows the prevalent coronary risk factors of the participants, according to their number of vessel diseased.

Predictive value of risk factors for angiographically CAD

Comparing the prevalence of risk factors between the CAD and non-CAD groups of our study population, and using multivariate binary logistic regression analysis, we examined the ability of every coronary risk factor to independently predict the angiographic presence of significant CAD. The results showed that classic established risk factors such as, age, male gender, hypertension, DM were still the important independent risk factors of CAD in our population. However, in this study, we could not find a significant association between CAD and smoking, dyslipidemia, obesity, and family history of CAD in the multivariate analysis.

It is noteworthy that this is the first, large-scale study showed chronic kidney disease (odds ratio [OR]=1.440, *P*=0.005) was found independent risk factor for CAD, while total bilirubin (odds ratio [OR]=0.959, P<0.001) was an independent protective factor for CAD. A detailed presentation of the relevant data is given in **Table 4**.

Discussion

To our knowledge, this is the first large-scale study that has primarily focused on the potential relationship between classic established or specific risk factors and coronary angiographic features. The findings of the present study relate to a representative group of consecutively investigated patients determined by cardiologists to require angiography. Thus, the variables associated with disease severity and the strength of associations we found may differ from patterns in the general population. The incidence of significant CAD will be lower in the general population than in our patient group, and the relation between risk factors and severity of disease will be less than noted here.

The association between the presence and severity of CAD and cardiovascular risk factors were evaluated in some studies. Our findings

Table 4. Results from multiple binary logistic regression analysis that evaluated the predictive value of risk factors for CAD

Risk factors	Odds ratio (95% confidence intervals)	*P* value
Age	1.053 (1.040-1.066)	0.000
Male gender	5.101 (1.735-15.002)	0.000
Hypertension	1.423 (1.112-1.821)	0.005
Diabetic mellitus	2.316 (1.589-3.376)	0.000
CKD	1.440 (1.414-1.860)	0.005
TBIL	0.959 (0.942-0.977)	0.000

Abbreviations: CKD, chronic kidney disease; TBIL, total bilirubin.

are largely comparable with those of Wang et al's [6] study, which enrolled 594 participants and showed that male gender, aging, hypertension, diabetes, and positive family history were independent risk factors for CAD in patients who underwent angiography in Australia. Recently, in one Chinese population sample, Jin et al. [7] explored the relationship between blood lipid levels and CAD severity quantified by the cumulative Gensini score and observed a strong positive correlation with mean levels of triglycerides and LDL-C. In another additional angiographic study, Ning et al. [8] suggested that multi-vessel disease (advanced CAD) were more likely in patients with older age and higher LDL-C levels, confirming the significant association of age and lipid abnormalities with angiographic CAD severity. These differences could be the results of variable clinical characteristics of the study population, inconsistently, examined risk factors, and coronary segments. Patients with acute ST-elevated myocardial infarction, previous myocardial infarction history, and previous coronary artery bypass surgery or angioplasty syndromes were excluded in our study population.

Interestingly, recent studies highlighted the existence of a paradoxical relationship between obesity and CAD. The obesity paradox issue has provoked considerable debate and the underlying mechanisms still remain obscure. Several studies [9-13], exploring this phenomenon in different populations, have produced contradictory data. In terms of CAD severity, Rubinshtein et al. [14] stated that obesity was an independent negative predictor of high-risk coronary anatomy at angiography, indicating that obese patients had a lower prevalence of severe coronary lesions. However, one study [15] from Texas suggested that obese patients undergoing angiography for clinically suspected CAD were more likely to demonstrate normal angiograms, accentuating the inverse relationship between obesity and angiographic CAD manifestations. In addition, several studies have questioned the impact of obesity on the presence and severity of CAD. The WISE study [16] investigators supported that among women undergoing angiography for suspected ischemia, BMI was not independently associated with angiographic CAD. In agreement with the above, Mehta et al. [17] identified no remarkable differences in the angiographic presence of multi-vessel disease between normal, overweight, and obese patients, whereas Niraj et al. [18] concluded that obesity, after adjustment for comorbidities, was not an independent predictor of coronary lesion severity. The finding of the present study is consistent with results observed by WISE study, and find that BMI was not associated with CAD. The obesity was not found to increase the possibility of being diagnosed with angiographically significant CAD but proved a poor determinant of CAD severity (containing the Gensini scores and Number of vessel ≥50% stenosis). The obesity was not an independent risk factor of CAD in this Chinese population.

There are few studies which have examined the relationship between family history of CAD and the presence of coronary artery disease defined by coronary arteriography. It is controversy about the role of positive family history as an independent risk factor for coronary artery disease. Recently, Hoseini et al. [19] in 2008 has reported findings that positive family history was a major risk factor for coronary artery disease which strongly predisposes to the atherosclerotic process at younger ages. However, some angiographic studies have noted only weak associations between family history and the severity of coronary atherosclerosis [20, 21]. This current study of patients undergoing angiography shows that the severity and extent of coronary artery disease to be not statistically different in patients with a family with history of CAD than in those without (3.13% and 3.23%, respectively; P=0.545), and we could not find a significant association between CAD and family history of premature CAD, in the multivariate analysis.

There are additional information for risk assessment in patients with CAD which could be provided by biochemical markers that serve as complementary predictors of atherosclerosis. Several studies had reported that low circulatory serum bilirubin levels were associated with an increased risk for coronary artery disease (CAD) or other atherosclerosis outcomes [22-27]. Schwertner et al. [28] were the first to observe a significant inverse correlation between total bilirubin plasma concentrations and the prevalence of CAD. This important finding indicated that a lower than normal serum bilirubin concentration is associated with the presence of ischemic heart disease. Subsequently, Hopkins et al noted that patients with early familial CAD have an average total serum bilirubin of 8.9~6.1 mmol/L compared with 12.4~8.1 mmol/L in healthy control subjects. In a prospective study in middle-aged British men, Breimer et al. [29] observed a U-shaped relationship between circulating bilirubin concentrations and cardiovascular risk, leading to the conclusion that low concentrations of serum bilirubin are associated with increased risk of ischemic heart disease. These and other investigators found that plasma bilirubin correlated inversely with several known risk factors for CAD, such as smoking, LDL-cholesterol, diabetes, and obesity, and correlated directly with the protective factor HDL-cholesterol [30, 31]. The reduced concentration of total bilirubin in plasma related univariately and multivariately to the presence of CAD, and this relationship remained significant after adjustment for known CAD risk factors such as age, cholesterol, HDL-cholesterol, smoking, and systolic blood pressure [31]. On the basis of these findings, low bilirubin was suggested as an independent risk factor for CAD, and an inverse correlation was demonstrated between bilirubin concentration and CAD morbidity. A study in healthy individuals grouped by low, intermediate and high serum bilirubin levels revealed that elevated bilirubin concentrations protect from coronary flow reserve impairment, coronary microvascular dysfunction, and possibly coronary atherosclerosis [32]. In the present study, although we did not adjust our findings for liver enzymes since these parameters were not available in the entire group. But we also observed similar results as described above, our data are in agreement with previous studies, suggesting that CAD patients presented a diminished concentration of total bilirubin. The high levels of total bilirubin is the protective factor of CAD in our selective participants.

It is well established that decreased renal function is associated with an increased frequency of cardiovascular disease [33]. However, it is unclear whether increased levels of serum creatinine is also associated with cardiovascular disease. The present study has found that CAD patients had higher creatinine level than non-CAD participants, and the 3-vessel group had the highest level among the four different vessel groups. This study also shows that creatinine is the independent risk factor of CAD. However, estimating kidney function from serum creatinine level has well-recognized limitations, including variation in creatinine production by age, gender, and race [34]. Finally, our analysis is based on observational data; therefore, we cannot rule out confounding from unmeasured factors to explain our results. The levels of serum creatinine could be related, for example, to other causes of kidney disease. The association between the levels of serum creatinine and incidence of CAD should be evaluated in a selective way.

Conclusion

Results of our study imply that, age, male gender, smoking, hypertension (or SBP), dyslipidemia, DM, LDL-C, FPG, and creatinine are independent risk factor of CAD, however, total bilirubin is an independent protective factor for CAD in this cohort of Chinese catheterized patients.

Acknowledgements

This work was supported by grants to Tang Cheng-chun from the Natural Science Foundation of China (research Grant #81370225).

Disclosure of conflict of interest

None.

Address correspondence to: Cheng-Chun Tang, Department of Cardiology, Zhongda Hospital of Southeast University Medical School, Nanjing 210009, China. E-mail: tangchengchun@medmail.com.cn

References

[1] Kannel WB, D'Agostino RB, Sullivan L and Wilson PW. Concept and usefulness of cardiovas-

cular risk profiles. Am Heart J 2004; 148: 16-26.
[2] Yusuf S, Reddy S, Ounpuu S and Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation 2001; 104: 2855-2864.
[3] Yusuf S, Reddy S, Ounpuu S and Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001; 104: 2746-2753.
[4] D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM and Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117: 743-753.
[5] Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983; 51: 606.
[6] Wang XL, Tam C, McCredie RM and Wilcken DE. Determinants of severity of coronary artery disease in Australian men and women. Circulation 1994; 89: 1974-1981.
[7] Jin Z, Zhang Y, Chen J, Zhu J, Zhang F, Qiu Y and Zhao L. Study of the correlation between blood lipid levels and the severity of coronary atherosclerosis in a Chinese population sample. Acta Cardiol 2006; 61: 603-606.
[8] Ning XH, Xiang XP, Lu N, Zhang YX, Wang WJ, Liu Y and Zhou Z. [Relation of risk factors to coronary artery stenosis severity in coronary atherosclerotic heart disease]. Zhonghua Yi Xue Za Zhi 2008; 88: 1267-1269.
[9] Afonso L, Niraj A, Veeranna V, Fakhry H and Pradhan J. Ethnic and sex differences in disease burden in patients undergoing coronary angiography: the confounding influence of obesity. Ethn Dis 2008; 18: 53-58.
[10] Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q and Pepine CJ. Obesity paradox in patients with hypertension and coronary artery disease. Am J Med 2007; 120: 863-870.
[11] Brandon LJ, Mullis RM, Jonnalagadda SS and Hughes MH. Relationships and CHD risks of BMI, lipoproteins, lipids, and blood pressure in African-American men and women. Prev Med 2005; 40: 349-354.
[12] Janssen I, Katzmarzyk PT and Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. Arch Intern Med 2002; 162: 2074-2079.
[13] Stalls CM, Triplette MA, Viera AJ, Pathman DE, Cohen MG and Rossi JS. The association between body mass index and coronary artery disease severity: a comparison of black and white patients. Am Heart J 2014; 167: 514-520.
[14] Rubinshtein R, Halon DA, Jaffe R, Shahla J and Lewis BS. Relation between obesity and severity of coronary artery disease in patients undergoing coronary angiography. Am J Cardiol 2006; 97: 1277-1280.
[15] Phillips SD and Roberts WC. Comparison of body mass index among patients with versus without angiographic coronary artery disease. Am J Cardiol 2007; 100: 18-22.
[16] Wessel TR, Arant CB, Olson MB, Johnson BD, Reis SE, Sharaf BL, Shaw LJ, Handberg E, Sopko G, Kelsey SF, Pepine CJ and Merz NB. Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women. JAMA 2004; 292: 1179-1187.
[17] Mehta L, Devlin W, McCullough PA, O'Neill WW, Skelding KA, Stone GW, Boura JA and Grines CL. Impact of body mass index on outcomes after percutaneous coronary intervention in patients with acute myocardial infarction. Am J Cardiol 2007; 99: 906-910.
[18] Niraj A, Pradhan J, Fakhry H, Veeranna V and Afonso L. Severity of coronary artery disease in obese patients undergoing coronary angiography: "obesity paradox" revisited. Clin Cardiol 2007; 30: 391-396.
[19] Hoseini K, Sadeghian S, Mahmoudian M, Hamidian R and Abbasi A. Family history of cardiovascular disease as a risk factor for coronary artery disease in adult offspring. Monaldi Arch Chest Dis 2008; 70: 84-87.
[20] Holmes DR, Elveback LR, Frye RL, Kottke BA and Ellefson RD. Association of risk factor variables and coronary artery disease documented with angiography. Circulation 1981; 63: 293-299.
[21] Hamby RI. Hereditary aspects of coronary artery disease. Am Heart J 1981; 101: 639-649.
[22] Novotny L and Vitek L. Inverse relationship between serum bilirubin and atherosclerosis in men: a meta-analysis of published studies. Exp Biol Med (Maywood) 2003; 228: 568-571.
[23] Djousse L, Rothman KJ, Cupples LA, Levy D and Ellison RC. Effect of serum albumin and bilirubin on the risk of myocardial infarction (the Framingham Offspring Study). Am J Cardiol 2003; 91: 485-488.
[24] Endler G, Hamwi A, Sunder-Plassmann R, Exner M, Vukovich T, Mannhalter C, Wojta J, Huber K and Wagner O. Is low serum bilirubin an independent risk factor for coronary artery disease in men but not in women? Clin Chem 2003; 49: 1201-1204.
[25] Troughton JA, Woodside JV, Young IS, Arveiler D, Amouyel P, Ferrieres J, Ducimetiere P, Patterson CC, Kee F, Yarnell JW, Evans A; PRIME

Study Group. Bilirubin and coronary heart disease risk in the Prospective Epidemiological Study of Myocardial Infarction (PRIME). Eur J Cardiovasc Prev Rehabil 2007; 14: 79-84.

[26] Lin JP, O'Donnell CJ, Schwaiger JP, Cupples LA, Lingenhel A, Hunt SC, Yang S and Kronenberg F. Association between the UGT1A1*28 allele, bilirubin levels, and coronary heart disease in the Framingham Heart Study. Circulation 2006; 114: 1476-1481.

[27] Rantner B, Kollerits B, Anderwald-Stadler M, Klein-Weigel P, Gruber I, Gehringer A, Haak M, Schnapka-Kopf M, Fraedrich G and Kronenberg F. Association between the UGT1A1 TA-repeat polymorphism and bilirubin concentration in patients with intermittent claudication: results from the CAVASIC study. Clin Chem 2008; 54: 851-857.

[28] Schwertner HA, Jackson WG and Tolan G. Association of low serum concentration of bilirubin with increased risk of coronary artery disease. Clin Chem 1994; 40: 18-23.

[29] Breimer LH, Wannamethee G, Ebrahim S and Shaper AG. Serum bilirubin and risk of ischemic heart disease in middle-aged British men. Clin Chem 1995; 41: 1504-1508.

[30] Schwertner HA. Association of smoking and low serum bilirubin antioxidant concentrations. Atherosclerosis 1998; 136: 383-387.

[31] Madhavan M, Wattigney WA, Srinivasan SR and Berenson GS. Serum bilirubin distribution and its relation to cardiovascular risk in children and young adults. Atherosclerosis 1997; 131: 107-113.

[32] Gullu H, Erdogan D, Tok D, Topcu S, Caliskan M, Ulus T and Muderrisoglu H. High serum bilirubin concentrations preserve coronary flow reserve and coronary microvascular functions. Arterioscler Thromb Vasc Biol 2005; 25: 2289-2294.

[33] Reis SE, Olson MB, Fried L, Reeser V, Mankad S, Pepine CJ, Kerensky R, Merz CN, Sharaf BL, Sopko G, Rogers WJ and Holubkov R. Mild renal insufficiency is associated with angiographic coronary artery disease in women. Circulation 2002; 105: 2826-2829.

[34] Perrone RD, Madias NE and Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992; 38: 1933-1953.