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Gender Differences in Types and Frequencies of Coronary Artery Anomalies and Myocardial Bridge in 10,457 Chinese Undergoing 320-Slice Computed Tomography

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Abstract: Varied frequencies of coronary artery anomalies (CAAs) and myocardial bridge (MB) exist in previous studies. Race and gender may play a role. The present study aimed to investigate the gender differences in types and frequencies of coronary artery anomalies (CAAs) and myocardial bridge (MB) in Chinese undergoing 320-slice coronary computed tomography. The authors assessed prospectively the records of 10,457 consecutive patients who underwent 320-slice coronary computed tomography for any reason. CAAs were divided into 4 groups: 1) Anomalies of origination; 2) Anomalies of intrinsic coronary arterial anatomy; 3) fistula; 4) Number anomalies. Clinical relevance based classifications of CAAs (Class I-Benign; II-Relevant; III-Severe; IV-Critical) were also presented. Types and frequencies of CAAs and MB were compared between males and females. The overall prevalence of CAAs was 2.60% in our study, involving 0.62% of anomalies of origination, 1.72% of anomalies of intrinsic coronary arterial anatomy, 0.23% of fistula, and 0.04% of number anomalies. Gender differences were not presented in the frequencies of the majority of CAAs ($p>0.05$). However, males were more likely to have LCX originating from the right sinus of Valsalva when compared with females (0.11% vs. 0.01%, $p=0.027$). There was no difference of clinical relevance based classifications of CAAs between males and females ($p>0.05$). The prevalence of MB was 33.15% (3466/10,475) in total. Higher frequency (19.13% vs. 14.0%, $p<0.001$) and longer average length (16.89±8.58mm vs. 13.71±8.50mm, $p<0.001$) of MB were observed in males than those in females; while the distribution and the mean depth of MB were similar in males and females ($p>0.05$). In conclusion, LCX originating from the right sinus of Valsalva and MB with longer average length occurred more frequently in Chinese males than females.

Keywords: Computed Tomography Angiography, Coronary Artery Anomaly, Myocardial Bridge, Fistula, Coronary Hypoplasia

1. Introduction

Although most coronary artery anomalies (CAAs) and myocardial bridge (MB) are thought to be benign, some of them can cause sudden death, syncope, severe arrhythmia, myocardial infarction and heart failure [1]. Conventional angiography is considered to be the gold standard for the diagnosis of CAAs and MB in clinical practice. Unfortunately, it cannot show reliably the complex three-dimensional natures of CAAs and MB. In addition, CAAs might increase the fluoroscopy time, catheters used and complications during the procedure [2]. Multi-slice computed tomography allows rapid acquisition of the entire 3D cardiac volume of data with excellent spatial resolution, and is considered to be

appropriate indication for patients with suspicious CAAs and MB [3-10].

The frequencies are reported to be approximately 0.3% to 2.9% for CAAs and 3.1% to 26% for MB in the general population undergoing multi-slice computed tomography [3-10]. Among multiple influencing factors, race and gender may play a role in the types and frequencies of CAAs and MB [5, 11, 12]. A study performed by Barriales Villa et al [11] showed that the incidence of CAAs was higher in the males than females in Asturias Principality, while Diez et al. [12] reported a contrary finding in American. Unfortunately, gender differences of CAAs and MB in Chinese were not documented before. In the present study, the authors aimed to investigate the gender differences in the types and frequencies of CAAs and MB in Chinese who underwent 320-slice coronary computed tomography.

2. Materials and Methods

The present study was approved by the Institutional Review Board, and the written informed consents were received from all patients undergoing 320-slice coronary computed tomography (Aquilion ONE; Toshiba Medical Systems, Ottawara, Japan) in our hospital from December 1, 2010 to December 31, 2015. A total of 10,457 consecutive patients were enrolled. The indications for performing 320-slice coronary computed tomography were evaluation of suspected coronary artery disease (depending on angina-like symptoms, cardiogenic syncope, elevated cardiovascular risk, abnormal echocardiogram, positive stress ECG test, positive myocardial perfusion scintigraphies), determination of the patency of bypass grafts or stents, evaluation of cardiomyopathy, and preoperative evaluation for non-coronary surgery.

320-slice CT examinations were performed with 0.5-mm detector elements, 350 ms of gantry rotation time, and up to 16 cm of coverage in Z direction. Tube voltage was set at 100~135 kV and the maximal tube current was 400-580 mA. Oral β-blocker (50-100mg metoprolol tablets; Astrazeneca, Wuxi, China) was given to patients with a resting heart rate >70 bpm before CT scan. Each patient received 0.5 mg nitroglycerin (nitroglycerine tablets; Yimin Pharma, Beijing, China) sublingually 2~4 min before CT scan, unless contraindicated. 50-100 ml nonionic iodinated contrast agent (Isovue-370; Bracco Diagnostics, Guangzhou, China) was injected intravenously at a flow rate of 6.0 ml.s-1, followed by a saline flush of 20 ml at a flow rate of 4.0 ml.s-1. Initial ECG gated datasets were reconstructed automatically at 75% of R-R interval, with a slice thickness of 0.50 mm and a reconstruction interval of 0.25 mm. Then, the anonymized datasets were transferred to an image workstation (Vitrea 2.0; Vital Images, Minnetonka, MN) for post processing and evaluation.

All 320-slice CT images were evaluated using a 15-segment classification model of the American Heart Association [13]. Cases with poor image quality were excluded from evaluation. The CT images of patients with CAAs were carefully assessed by two experienced radiologists (with more than 4 years of experience in cardiac CT) and one experienced cardiologists. If there was a discrepancy among three reviewers, reading session was organized to reach a consensus.

Currently, the definition of normality and abnormality of coronary artery has not yet been completely clarified and no generally accepted CAAs classification exists. Some researchers classify coronary anomalies based on their hemodynamic significance, while others believe in exclusively anatomic classification [4]. Based on the classification reported by Angelini et al [14], the authors in the present study defined and classified the CAAs according to a modified classification divided into 4 groups: 1) Anomalies of origination: aortic and nonaortic; 2) Anomalies of intrinsic coronary arterial anatomy: coronary atresia, coronary hypoplasia, coronary aneurysms and intercoronary communications; 3) Anomalies of termination: coronary artery fistula; 4) Number anomalies: single coronary artery, dual coronary arteries and absent coronary artery. Clinical relevance based classification (Class I-Benign; II-Relevant; III-Severe; IV-Critical) were also presented for CAAs [15]. Identification of MB was determined by two conditions: 1) the presence of the "step-down and step-up" appearance, namely, a significant tortuosity of the segment beneath MB at the entrance (step-down) and the exit (step-up) sites, the same as the findings by angiography; 2) soft tissue density covering the coronary artery, which had the same contrast enhancement as myocardial tissue [16]. The authors formed a male and a female group to compare the types and frequencies of the CAAs and MB between two groups.

Statistical analysis was performed by using SPSS 18.0 for Windows (SPPS Inc, Chicago, IL, USA). Continuous variables were presented as means ± standard deviation. Categorical variables were expressed as percentages. Student's *t*-test or the Mann-Whitney *U* test were used to compare continuous variables, while the chi-square test or Fisher's exact test were used to compare categorical variables. For all the tests, $p<0.05$ was considered to be statistically significant.

3. Results

The baseline characteristics of patients with CAAs and MB were listed in Table 1. There were 2165 (57.92%) men and 1573 (42.08%) women. The mean patient age was 59.9±12.2 years. Males were younger than females on average ($p<0.001$). There was no significant difference between two groups with respect to body mass index and the incidences of hypertension, diabetes, dyslipidemia and family history of coronary artery disease. The percentage smoker/ex-smoker was higher in the males than the females ($p<0.001$).

Table 1. *Baseline characteristics of subjects with coronary artery anomalies and myocardial bridges.*

Characteristics	Overall (n=3738)	Male (n=2165)	Female (n=1573)	p-value
Age, years	59.9±12.2*	58.0±12.8	62.5±10.9	<0.001
BMI, kg/m^2	24.3±2.9	24.1±2.8	24.5±2.9	0.141
Diabetes, n(%)	1897 (50.75)	1085 (29.03)	812 (21.72)	0.363
Hypertension, n(%)	2502 (66.93)	1398 (37.40)	1004 (29.53)	0.639
Dyslipidemia, n(%)	1827 (48.88)	1054 (28.20)	773 (20.68)	0.782
Smoker/Ex-smoker, n(%)	1083 (28.97)	842 (22.52)	241 (6.45)	<0.001
Family history of CAD, n(%)	528 (14.12)	295 (7.89)	233 (6.23)	0.304

*Data are means±standard deviations
Abbreviations: BMI, body mass index; CAD, coronary artery disease.

Types and frequencies of CAAs were summarized in Table 2. Overall, the frequency of CAAs was 272/10, 457 (2.60%), including 64 (0.62%) anomalous origin of coronary artery, 180 (1.72%) anomalies of intrinsic coronary arterial anatomy, 24 (0.23%) coronary artery fistula, and 4 (0.04%) number anomalies of coronary artery. The overall prevalence of the CAAs was similar in the males and females (1.57% vs. 1.03%, p=0.132). Furthermore, clinical relevance based classifications of CAAs were similar in the males and females. (Table 3)

Table 2. *Gender differences in types and frequency of coronary artery anomalies.*

Types of anomalies	Class*	Number of patients, n	Frequency, %	Male, n	Female, n	p-value
Total CT angiography	…	10457	…	5837	4620	…
Total anomalies	…	272	2.60	164	108	0.132
1a. Anomalies of origination (aortic)	…	55	0.53	36	19	0.149
High take-off of the RCA	I	14	0.13	11	3	0.148
LAD-LCX originating from separate ostia	I	1	0.01	0	1	0.442
RCA originating from the left sV	III	27	0.26	13	14	0.422
LCX originating from the right sV	I	12	0.11	11	1	0.027
LMCA originating from the right sV	III	1	0.01	1	0	1.00
1b. Anomalies of origination(nonaortic)	…	9	0.09	6	3	0.749
LAD originating from the RCA	ND	1	0.01	0	1	0.442
LCX originating from the RCA	I	5	0.05	3	2	1.00
RCA originating from the LAD	ND	3	0.03	3	0	0.260
2. Anomalies of intrinsic coronary arterial anatomy	…	180	1.72	105	75	0.493
Coronary atresia	II	1	0.01	0	1	0.442
Coronary hypoplasia	II	129	1.23	73	56	0.859
Coronary aneurysms (saccular)	ND	43	0.41	28	15	0.219
Intercoronary communications	ND	7	0.07	4	3	1.00
3. Anomalies of termination (fistula)	…	24	0.23	14	10	0.804
LAD-pulmonary artery	II	4	0.04	3	1	0.788
RCA-pulmonary artery	II	3	0.03	3	0	0.260
LMCA-pulmonary artery	II	1	0.01	1	0	1.00
Conus- pulmonary artery	II	13	0.12	5	8	0.207
LCX-right atrium	II	1	0.01	0	1	0.442
RCA-right atrium	II	1	0.01	1	0	1.00
RCA-left ventricle	II	1	0.01	1	0	1.00
4. Number anomalies	…	4	0.04	3	1	0.788
Dual LAD	I	1	0.01	0	1	0.442
Absent LCX	II	2	0.02	2	0	0.507
Absent RCA	II	1	0.01	1	0	1.00

*Clinical relevance based classification: Class I-Benign, II-Relevant, III-Severe, IV-Critical. Class IV was defined as Class II or III superimposed with coronary artery disease, which was not discussed in the present study.
Abbreviations: CT, computed tomography; ND, not defined; sV, sinus of Valsalva; LMCA, left main coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 3. *Gender differences in the clinical relevance based classifications of coronary artery anomalies.*

Classification	Total (n=272)	Male (n=164)	Female (n=108)	p
I-Benign	33	25	8	0.053
II-Relevant	157	90	67	0.242
III-Severe	28	14	14	0.240
Not defined	54	35	19	0.448

Among anomalous origin of coronary artery, RCA originating from the left sinus of Valsalva (sV) (n=27, 0.26%), high take-off of the RCA (n=14, 0.13%) and LCX originating from the right sV (n=12,0.11%) were the top three types of anomalies. (Table 2, Figure 1) The percentage of LCX originating from the right sV was significant higher in the males than the females (0.11% vs. 0.01%, p=0.027). However, the authors determined no gender differences in the other types of anomalous origin (p>0.05).

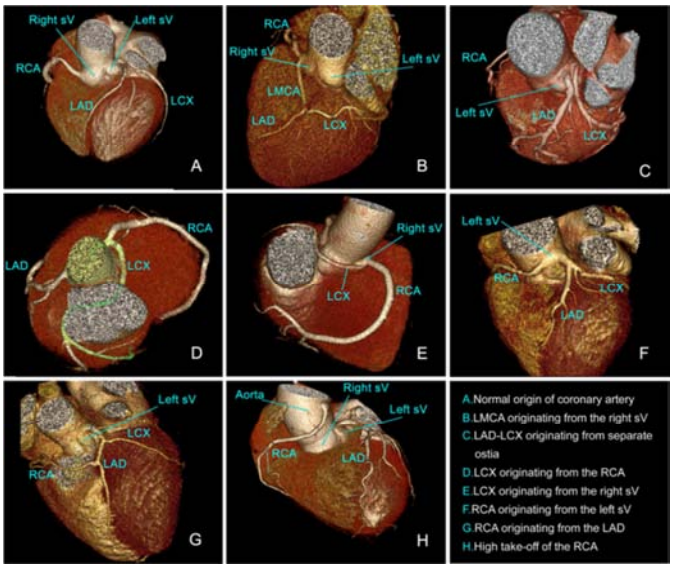

Figure 1. *320-slice CT images of anomalous origin of coronary artery. A. Normal CT anatomy of the coronary arteries: The right coronary artery (RCA) that arises from the right sinus of Valsalva (sV) and the left main coronary artery (LMCA) that arises from the left sV and bifurcates into the left anterior descending artery (LAD) and left circumflex artery (LCX). B. CT image of a 47 years old male with LMCA originating from the right sV. C. CT image of a 72 years old female with separate ostia of LAD and LCX from the left sV. D. CT image of a 62 years old male with LCX originating from the RCA. E. CT image of a 57 years old with a hypoplastic LCX originating from the right sV. F. CT image of a 69 years old female with the RCA originates anomalously from the left sV. G. CT image of a 62 years old male with RCA originating anomalously from the LAD. H. CT image of a 62 years old male with the RCA originates anomalously from the ascending aorta.*

Among anomalies of intrinsic coronary arterial anatomy, no significant gender differences were presented in the frequencies of coronary atresia (0% vs. 0.01%, p=0.442), hypoplasia (0.70% vs. 0.54%, p=0.859) and aneurysms (0.27% vs. 0.14%, p=0.219). (Table 2, Figure 2-3)

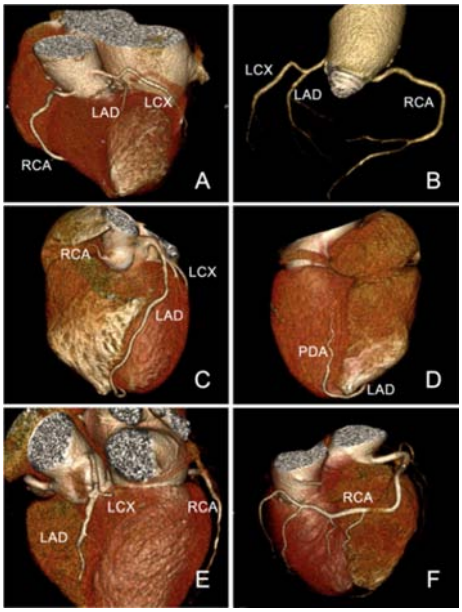

Figure 2. *320-slice CT images of coronary hypoplasia. A&B. CT images of a 64 years old male with rheumatic heart disease, indicating atrial hypertrophy and hypoplasia of the left anterior descending artery (LAD) and left circumflex artery (LCX). C&D. CT images of a 46 years old male suffering from recurrent syncope for one year, showing remarkable hypoplasia of the right coronary artery (RCA). The LAD reaches the posterior interventricular groove and connects with posterior descending artery. However, a 50% stenosis and a myocardial bridge with length of 14mm are presented in middle LAD, which might cause myocardial ischemia and syncope. E&F. CT images of a 68 years old female suffering from chest distress for one year, indicating hypoplasia of the LCX and mid-distal LAD. The blood supply of the left heart was compensated by the RCA.*

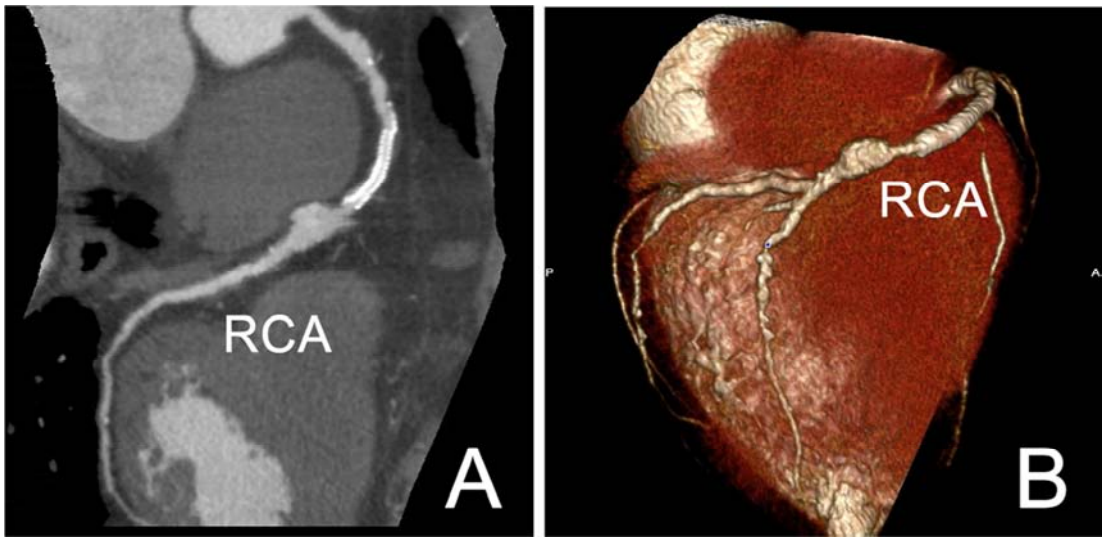

Figure 3. *320-slice CT images of a 76 years old male shows a coronary aneurysm in middle right coronary artery (RCA). A stent was implanted anterior to the aneurysm for significant stenosis of coronary artery.*

A total of 24 fistulas were observed in the present study. (Table 2, Figure 4-6) 21 of them were terminated to pulmonary artery, while 3 of them were terminated to right atrium or left ventricle. The authors found no significant gender difference in the frequency of fistulas (0.14% vs. 0.10%, p=0.804).

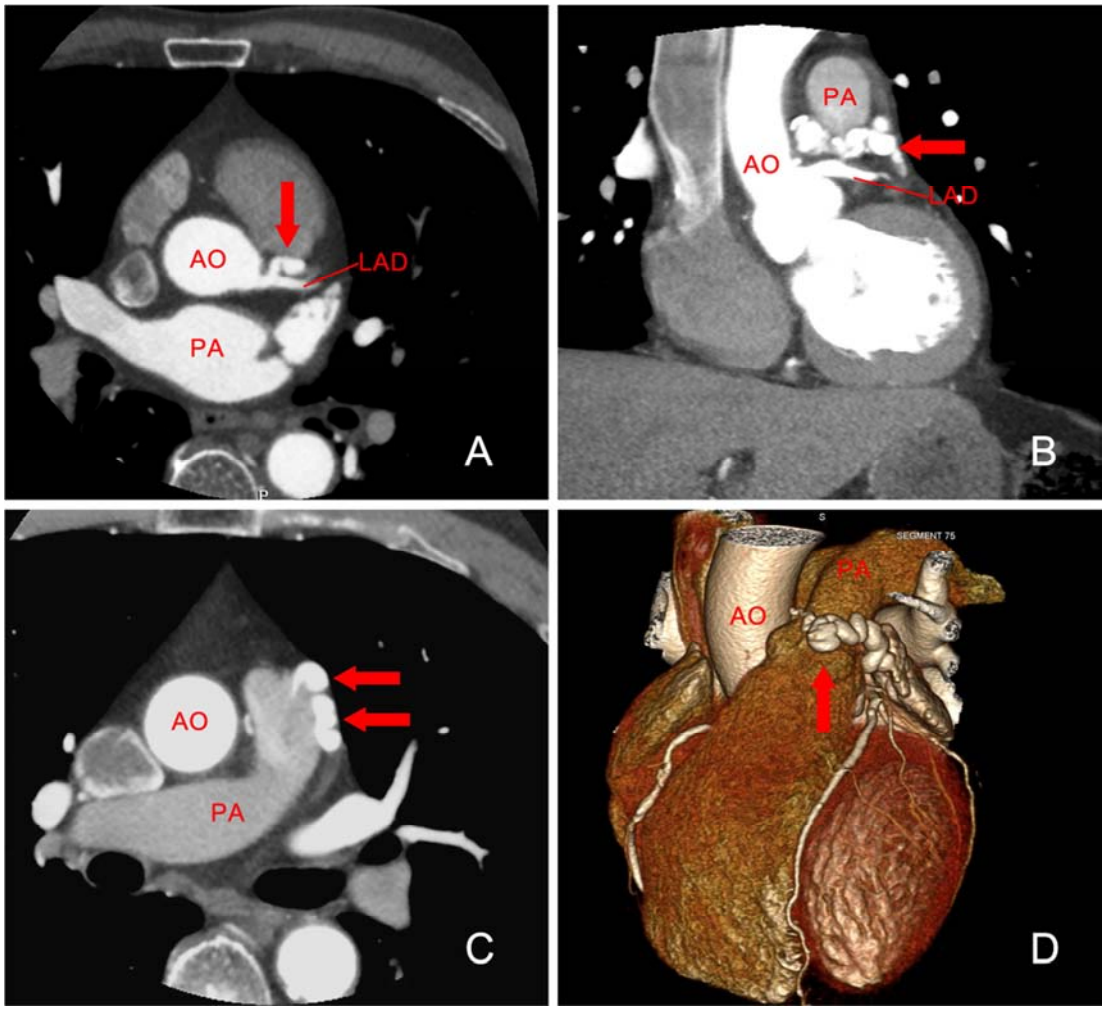

Figure 4. *320-slice CT images of LMCA-PA fistula in a 76 years old male, showing a plexus of fine tortuous vessels (B&D) arising from the LAD (A) and draining into PA (C). Abbreviations: LMCA, left main coronary artery; PA, pulmonary artery; AO, aorta; LAD, left anterior descending artery.*

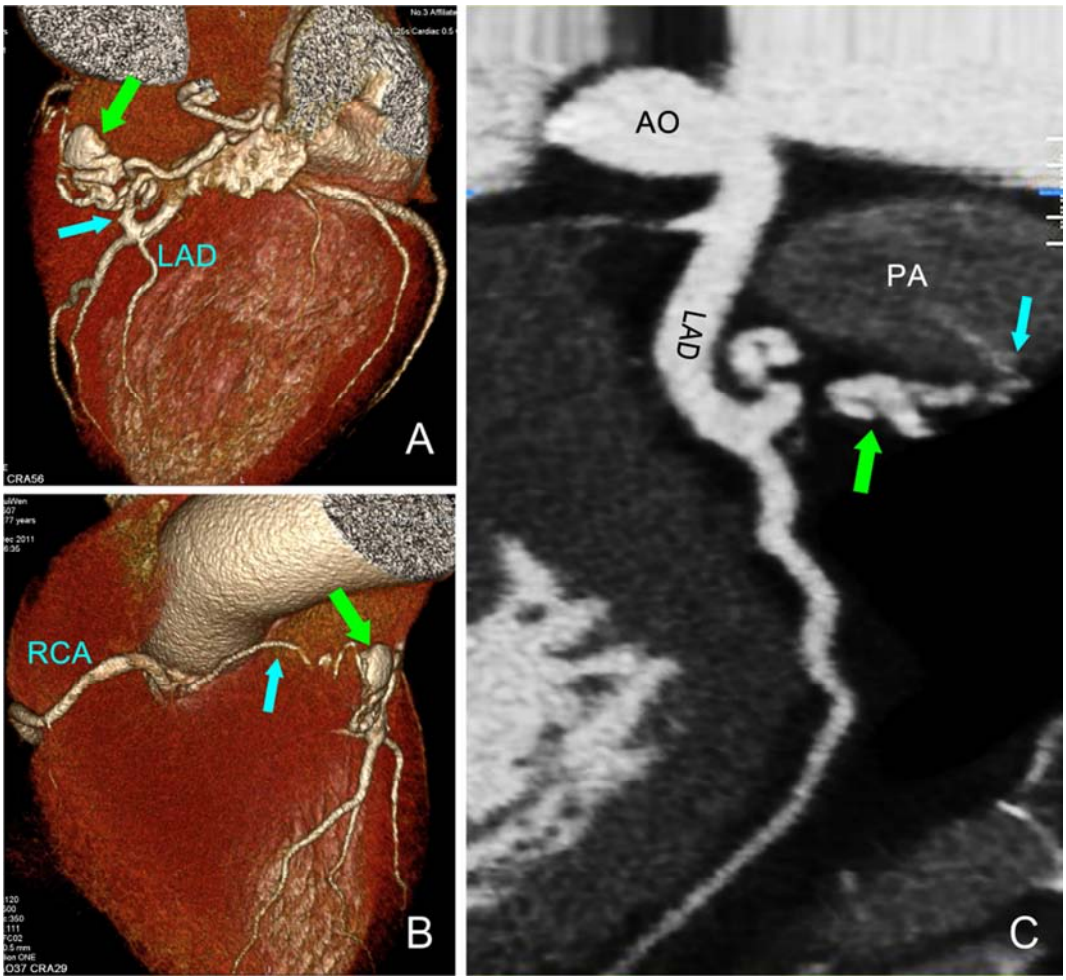

Figure 5. *320-slice CT images of LAD-PA-RCA fistula in a 77 years old male. A plexus of fine tortuous vessels arises from both the LAD (A) and RCA (B). Maximum intensity projection (C) demonstrates a flow jet to the PA through the fistula. Abbreviations: LMCA, left main coronary artery; PA, pulmonary artery; AO, aorta; LAD, left anterior descending artery; RCA, right coronary artery.*

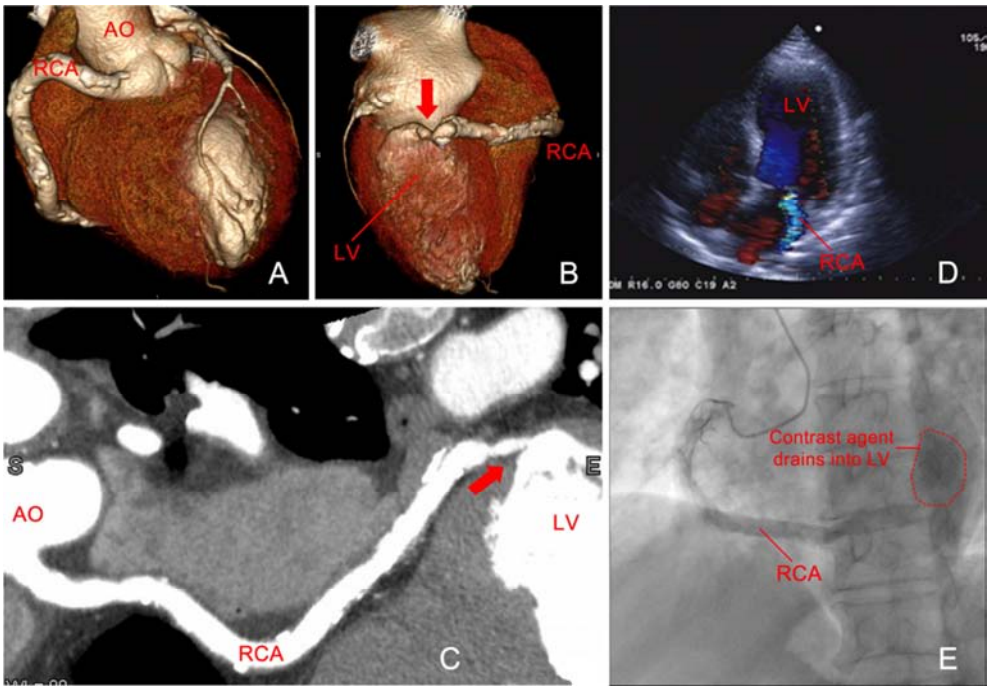

Figure 6. *320-slice CT images of RCA-LV fistula in a 71 years old male. The RCA is remarkably dilated (A&C) and drains into LV (B&C). These fistula is also detected by echocardiography (D) and conventional angiography (E). Abbreviations: AO, aorta; RCA, right coronary artery; LV, left ventricle.*

Number anomalies of coronary were rare. Only one case with dual coronary arteries and three cases with absent coronary artery were observed in the present study. (Table 2, Figure 7) Similarly, no marked difference was presented in the frequency of number anomalies between the males and females (0.03% vs. 0.01%, p=0.788).

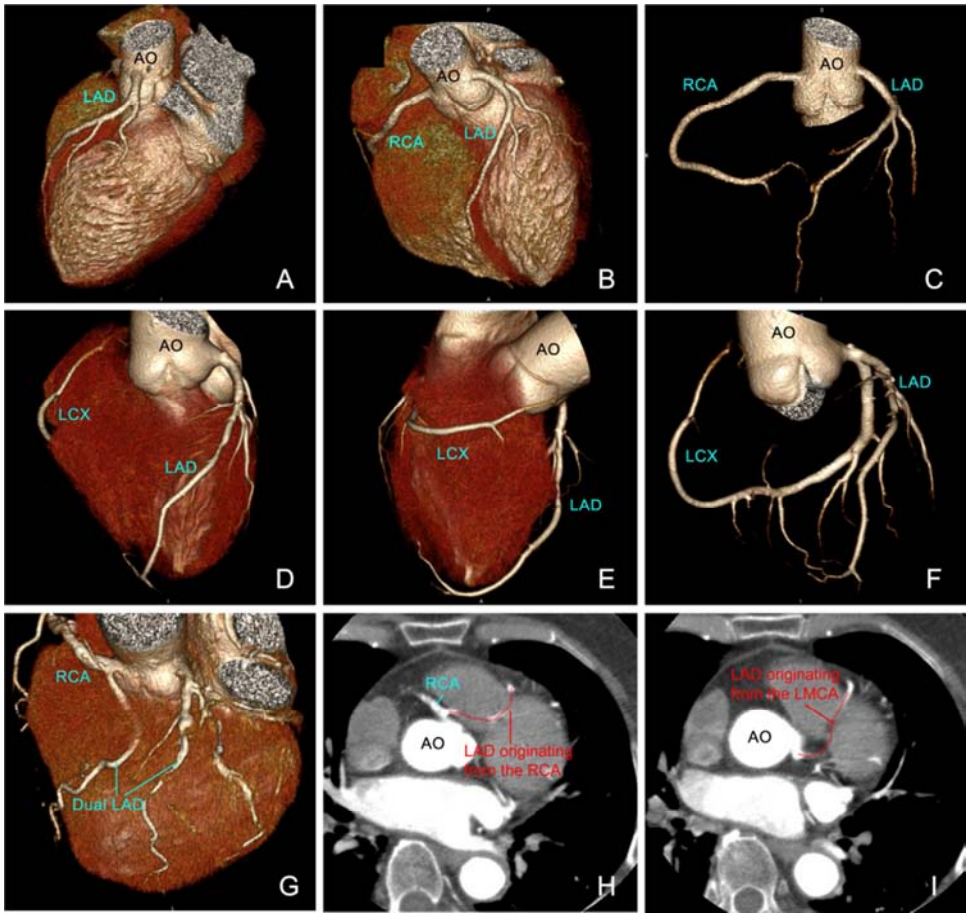

Figure 7. *320-slice CT images of number anomalies of coronary artery. A-C shows absent LCX in a 47 years old male suffering from chest discomfort for 4 months. No significant stenosis of coronary arteries is observed. D-F shows absent RCA in a 71 years old male suffering from syncope for 6 hours. The blood supply of the right heart is compensated by the extended LCX and LAD. However, a 60% stenosis in middle LAD is observed. G-I shows dual LAD in a 75 years old female. One LAD originates normally from the LMCA (I), and the other LAD originates anomalously from the RCA (H) and courses between PA and RV (G). Abbreviations: AO, aorta; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; PA, pulmonary artery; RV, right ventricle.*

Table 4. *The location, length and depth of myocardial bridge in the males and females.*

Myocardial bridge	Total (n=3466)	Male (n=2001)	Female (n=1465)	p
Overall	3466	2001	1465	<0.001
LAD	3170	1841	1329	0.180
LCX	225	136	89	0.394
RCA	37	20	17	0.649
LMCA	8	6	2	0.528
LAD & LCX	21	13	8	0.698
LAD & RCA	5	3	2	1.00
Length of myocardial bridge, mm	15.54±8.69	16.89±8.58	13.71±8.50	<0.001
Depth of myocardial bridge, mm	2.15±1.18	2.17±1.19	2.13±1.17	0.278

Abbreviations: sV, sinus of Valsalva; LMCA, left main coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

The frequency of MB was 33.15% (3466/10,475) in total, which was significant higher in the males than the females (19.13% vs. 14.0%, p<0.001). (Table 4) The authors further assessed the location, length and depth of MB in the males and females. 91.60% (3170/3466) of the MB were resided in LAD. Despite significant gender difference in frequency was presented, the distribution of MB resided in coronary arteries was similar between the males and females (92.0% vs. 90.7%, p>0.05). The mean length and depth of MB were 15.54±8.69 mm and 2.15±1.18 mm. The average length of MB was significant longer in the males than the females (16.89±8.58 mm vs. 13.71±8.50 mm, p<0.001), while the depth of MB were similar between two groups (2.17±1.19 mm vs. 2.13±1.17 mm, p=0.278).

4. Discussion

The present study is the first attempt to determine the gender differences of CAAs and MB in Chinese detected by

320-slice computed tomography. The overall incidences of CAAs and MB were 2.60% and 33.15%, which are similar to those of the previously reported studies [3-10]. No gender difference was presented in most of CAAs, except anomaly of LCX originating from the right sinus of Valsalva, which occurred more frequently in the males than females. Furthermore, higher frequency and longer average length of MB were observed in the males than those in the females.

Anomaly of intrinsic coronary arterial anatomy (1.72%) was the most common type of CAAs in the present study, including 1.23% of coronary hypoplasia. Hypoplastic coronary artery refers to congenital underdevelopment of one or more epicardial coronary arteries or their major branches with greatly decreased luminal diameter or length. Previous literatures considered it as a rare congenital abnormality with a high rate of sudden death and poor outcome [17]. However, most of these literatures are case reports and the diagnosis is often made at autopsy. Coronary hypoplasia has rarely been documented in living patients. Interestingly, the current study found a high frequency of coronary hypoplasia (1.23%) in Chinese adults. Actually, many cases with hypoplasia in a specific local region of coronary artery do not appear in signs, symptoms, or complications, and may therefore go unrecognized in clinical practice. A study reviewing 7500 coronary angiography records found the percentage of hypoplastic right coronary artery was as high as 6.2% [18]. It should be keep in mind that hypoplastic coronary artery can be asymptomatic, but is sometimes associated with myocardial infarction and sudden cardiac death under stress or intense physical activity. After non-invasive anatomic assessment by coronary computed tomography angiography, stress perfusion studies should always follow for further functional assessment.

Anomaly of origination is another common type of CAAs in both previous [3-8] and present studies. Majority of studies in the other nations reported anomaly of LAD-Cx originating from separate ostia (Class I-Benign) as the most common anomaly of origination. However, such cases were rare in Chinese population in the current study and previous study reported by Cheng et al [7]. This finding is favorable for Chinese physicians interested in coronary angiography, since they are less worry about the catheter-related complications caused by this anomaly. Anomaly of RCA originating from the left sV (Class III-Severe) was the most common anomalous origin of coronary artery in the present study, followed by anomalies of high take-off of the RCA (Class I-Benign), LCX originating from the right sV (Class I-Benign) and nonaortic nomalies of origination. It was reported that the fluoroscopy time, the mean number of catheters used, and the mean number of images obtained during the conventional angiography were higher in anomaly of RCA originating from the left sV when compared with the other anomalies. Consequently, increased patient radiation, radiopaque exposure and costs are required. Unlike study reported by Aydar et al [18], no gender difference was showed in most of anomalies of origination, except anomaly of LCX originating from the right sV, which occurred more frequently in the males. Awareness of the various presence of anomalous origination in different races and gender is critical for optimizing catheterization, which reduces the catheter-related complications.

Coronary artery fistulas consist of a communication between a coronary artery and a cardiac chamber or a great vessel. The most common type of fistula in the present study was the coronary-pulmonary artery type. The fistula is not clinically important in the majority of cases, especially in the early phase. But later on, it might produce coronary steal phenomenon (blood diverting from the high resistance myocardial capillary bed into the low resistance fistula), leading to angina, syncope, congestive heart failure, myocardial infarction and sudden death [19, 20]. The authors found no significant gender difference in the frequency of fistulas between males and females.

Number anomalies of coronary are rare in both present and previous studies [3-10]. Dual LAD is generally classified as benign, while single and absent coronary artery can cause ischemia and sudden death. The present study found one case with dual LAD and three cases with absent coronary artery. CT images can provide multiple angles and dimensions to properly expose and indentify the aortic root, coronary artery and pulmonary artery, which is important for evaluating whether another coronary artery ostium exists.

Although clinical relevance based classification has considered MB as Class I-Benign [15], it is reported recently that MB may have caused ischemia, coronary spasm, acute coronary syndrome, rupture of ventricular septum, arrhythmia, sudden death and complications during cardiac surgery [21]. Prevalence of MB was varying from 40% to 80% in autopsy series, 0.5% to 16% in conventional angiographic studies, and 3.1% to 26% in CT angiographic series [9, 10]. The prevalence of MB in the present study was as high as 33.15%. The difference in prevalence implies a relatively low diagnostic sensitivity of conventional angiography, in which the detection of MB depends on indirect signs (i.e., milking effect and/or the step down-step up phenomenon). CT angiography is an alternative and non-invasive method for accurate demonstration of the anatomical characteristics of MB. In the current study, majority of MB were located on the LAD in both males and females. However, the percentage of MB was significant higher in the males than the females. Despite similar average depth of MB was presented, the average length of MB was significant longer in the males than the females, which is consistent with the previous study approved by Aydar et al [18]. However, the exact clinical significance of this finding remains unclear. Whether increase in the frequency and length of the myocardial bridges in the males will lead to more coronary atherosclerosis and worse long-term prognosis should be investigated in the future.

There are several limitations in the present study: 1) In most patients, coronary artery anomalies are detected incidentally during the management of coronary artery disease. CT angiography cannot be used for prospective prevalence studies in general population because of ethical issues. 2) The mean age of the patients was relatively high. This may indicate a relatively benign nature of the anomalies that were

observed in these individuals. Anomalies in young adults with typically ischemic-sounding chest pain or syncope are more important to be identified. 3) CT angiography is associated with substantial irradiation [22] and contrast media nephropathy of the patients [23]. Studies demonstrated that 320-slice CT can reduce the radiation explosion and contrast doses when compared to 64-slice CT [23, 24].

5. Conclusion

In conclusion, 320-slice CT coronary angiography is a non-invasive technique for detecting CAAs and MB. Although no gender differences were showed in most of CAAs, anomaly of LCX originating from the right sV and MB with longer average length occurred more frequently in the males than the females.

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