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Coronary artery fistula with or without aneurysm: A large comparative study

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A R T I C L E I N F O

Keywords:
Coronary artery fistula
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A B S T R A C T

Background: The knowledge of coronary artery fistula (CAF) with coronary aneurysm mostly comes from case reports and is very limited. However, the management of CAF with and without aneurysm is different, more understanding of its clinical and imaging features is necessary. This is the first research focus on it through a large comparative study.
Purpose: To investigate the differences in imaging and clinical features of CAF with and without aneurysms.
Methods: We reviewed 96,037 consecutive patients undergoing coronary computed tomography angiogram (CCTA) between 2016 and 2020 and total of 429 CAF adult patients were enrolled. Those patients were divided into the CAF with aneurysm group (321 cases, 74.83%) and CAF without aneurysm group (108 cases, 25.17%) according to whether complicated with coronary aneurysm. Clinical baseline data, electrocardiographic (ECG) characteristics, the presence or absence of coronary atherosclerosis, complication symptoms and fistulous origin, entry site, number and diameter were analyzed. Chi-square test, T-test, Mann-Whitney U tests, and logistic regression analysis were performed.
Results: Most of the clinical baseline data did not differ significantly between the two groups ($P > 0.05$). However, heart murmur, coronary atherosclerosis, infective endocarditis (IE), fistulous diameter and fistulous entry site were significantly different ($P < 0.05$). Further multivariate logistic regression analysis showed that large fistulous diameter and coronary-cardiac chamber arterial fistulas was dependent risk factors for CAF complicated with aneurysm.
Conclusion: CAF patients with aneurysm were more prone to develop heart murmur than those patients without aneurysm. Different from other sites of aneurysms, coronary atherosclerosis is more common in CAF without aneurysm. Larger fistulous diameter and coronary-cardiac chamber arterial fistula are dependent risk factors for CAF with aneurysms.

Abbreviations: CAF, coronary artery fistula; CCTA, coronary computed tomography angiogram; ECG, electrocardiographic; IE, infective endocarditis; PA, pulmonary artery; CS, coronary sinus; LAD, left anterior descending; LCX, left circumflex artery; LM, left main coronary artery; RCA, right coronary artery.

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1. Introduction

Coronary artery fistula (CAF) is a rare congenital or acquired coronary artery anomaly, which is defined as any coronary artery anomaly draining into the cardiac cavity or other adjacent vascular structures [1]. Aneurysmal changes associated with CAF are defined as abnormal focal dilatation of the coronary artery exceeding to 1.5 times the diameter of the adjacent normal segment [2]. It can lead to bleeding, cardiac tamponade, and even death when a coronary aneurysm breaks into the pericardium [3]. Most of the reports on CAF with aneurysms are case reports, and there is no report on the cooperative study of CAF with or without aneurysm. Up to now, the differences in the natural course and imaging features of CAF with and without aneurysms are unclear, and there is a lake of clinical consensus on the treatment and surgical approach for both. In this study, we explored the characterization of CAF patients with and without aneurysms and aims to improve the knowledge and clinical management of CAF.

2. Materials and methods patients

This study was designed and conducted in compliance with the Health Insurance Portability and Accountability Act and approved by our institutional review board who waived need for informed consent considering the retrospective nature of the study. This study was registered on Clinical Trial Registry (Number:2022-B005) simultaneously. Consecutive 96,037 patients who underwent CCTA between 2016 and 2020 and met the following inclusion criteria were collected. Inclusion criteria: (1) diagnosis of CAF from CCTA (CAF refers to the abnormal connection between the coronary artery and any cardiac chamber or large vessels (including the superior vena cava, pulmonary artery [PA], pulmonary vein, or coronary sinus [CS]) [4]); (2) age > 18; (3) the image quality met the diagnostic requirements; (4) complete and available clinical data. Our final patient population consisted of 429 patients.

All medical history data were obtained through self-report of patients and medical record review before the CCTA scanning. ECG parameters were acquired from ECG diagnosis reports.

Table 1
Clinical and imaging characteristics [n (%)/$'x \pm s$/M($P25$, $P75$)].

	Total N = 429	CAF with aneurysm group N = 108	CAF without aneurysm group N = 321	$t/Z/\chi^2$	P value
Age	55.16 ± 11.88	55.69 ± 12.93	54.98 ± 11.52	0.532	0.595
Chest pain	121 (28.21)	31 (28.7)	90 (28.04)	0.018	0.894
Chest tightness	176 (41.03)	40 (37.04)	136 (42.37)	0.949	0.330
Palpitation	163 (38.00)	34 (31.48)	129 (40.19)	2.600	0.107
Shortness of breath	50 (11.66)	16 (14.81)	34 (10.59)	1.400	0.237
Dizziness	28 (6.53)	6 (5.56)	22 (6.85)	0.223	0.637
Heart murmur	16 (3.73)	11 (10.19)	5 (1.56)	16.753	< 0.001*
IE	26 (6.06)	11 (10.19)	15 (4.67)	4.313	0.038*
Pathological Q waves,	15 (3.50)	4 (3.70)	11 (3.43)	0.018	0.892
Atrial premature beat or atrial fibrillation	108 (25.17)	32 (29.63)	76 (23.68)	1.521	0.218
Ventricular premature beat or ventricular Tachycardia	83 (19.35)	26 (24.07)	57 (17.76)	2.067	0.151
Escape rhythm or heart block	40 (9.32)	11 (10.19)	29 (9.03)	0.127	0.722
Sinus arrhythmia	57 (13.29)	16 (14.81)	41 (12.77)	0.293	0.589
ST-T changes or Poor R-wave progression	127 (29.60)	37 (34.26)	90 (28.04)	1.501	0.220
Fistulous origin				6.117	0.526
LM	5 (1.17)	2 (1.85)	3 (0.93)		
LAD	168 (39.16)	38 (35.19)	130 (40.50)		
LCX	13 (3.03)	4 (3.70)	9 (2.80)		
RCA	125 (29.14)	30 (27.78)	95 (29.60)		
LAD + LCX	1 (0.23)	0 (0.00)	1 (0.31)		
LAD + RCA	110 (25.64)	30 (27.78)	80 (24.92)		
LCX + RCA	3 (0.70)	2 (1.85)	1 (0.31)		
LAD + LCX + RCA	4 (0.93)	2 (1.85)	2 (0.62)		
Fistulous entry site				9.068	0.011*
PA	377 (87.88)	87 (80.56)	290 (90.34)		
Cardiac chamber	50 (11.66)	21 (19.44)	29 (9.03)		
CS	2 (0.47)	0 (0.00)	2 (0.62)		
Fistulous number				0.340	0.952
1	333 (77.62)	82 (75.93)	251 (78.19)		
2	77 (17.95)	21 (19.44)	56 (17.45)		
3	16 (3.73)	4 (3.70)	12 (3.74)		
4	3 (0.70)	1 (0.93)	2 (0.62)		
Fistulous diameter (mm)	2.76 ± 2.07	3.51 ± 2.80	2.51 ± 1.70	4.453	< 0.001*
Coronary atherosclerosis	220 (51.28)	46 (42.59)	174 (54.21)	4.362	0.037*

IE, infective endocarditis; LM, left main coronary artery; LAD, left anterior descending; LCX, left circumflex artery; RCA, right coronary artery; PA, pulmonary artery; CS, coronary sinus; $*P < 0.05$ was used to indicate statistical significance.

2.1. CCTA acquisition

All patients underwent CCTA using a prospective ECG-triggered or retrospective ECG-gated. In participants with initial pre-scan heart rate >75 bpm, 25–50 mg β-blocker (Betaloc ZOK; AstraZeneca) were administered orally 1h before scan. Patients were routinely prepared for coronary examination, trained to breathe, and were asked to hold their breath for 10 s. Double tube high-pressure syringe was used to inject 65–85 ml contrast medium and 30 ml normal saline through the median cubital vein at the rate of 4–5 ml/s. The imaging scheme was as follows: tube voltage, 120 kV; tube current, 600 maps; rotation time, 0.42 s/r, Pitch 0.3; and thickness, 0.67 mm. The scanning range was extended from 1 cm below the tracheal carina to 2 cm below the diaphragm.

2.2. Image reconstruction and analysis of CCTA

The images were transferred to Philips workstation (cardiac examination and comprehensive cardiac analysis). All analyses steps and results were performed jointly by consensus between two radiologists with more than 5 years of experience. Disputes between the radiologists were decided by mutual agreement. The analysis features and parameters included with and without aneurysm, whether coronary atherosclerosis, fistulous origin, entry site, number, and diameter of fistula. Diagnosis criteria of CAF with aneurysm: In adults, the standard inner diameter of the coronary arteries is 3–6 mm. Based on the criteria, aneurysms are those whose diameter is 1.5 times that of the largest adjacent normal segment of the vessel, and the length of the dilated vessel does not exceed 1/3 of its overall length. CAF patients were divided into CAF with aneurysm group and CAF without aneurysm group according to whether accompanied with aneurysms. Diagnosis criteria of coronary atherosclerosis: In each coronary artery, coronary atherosclerosis was defined as any tissue structures of > 1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself [5]. To reduce the error in manual measurements of fistulous diameter, we took the average of two radiologists measured and retook the measurements if there were significant differences between the results. In this step, the both radiologists were blind to patients' baseline characteristics and the other's measurement results.

2.3. Statistical analysis

SPSS Statistics 23.0 (IBM Corp. Armonk, NY, USA) was used for all data analysis. Chi-squared tests or Fisher's exact tests were used for categorical variables. Independent sample T-test and the Mann-Whitney U tests for normally distributed and non-normally distributed continuous variables, respectively. All continuous variables were expressed as mean ± standard deviation (M ± SD). Categorical variables were represented as N (%). Logistic regression analyses were used to identify risk or protective factors of CAF with aneurysm. $P < 0.05$ (bilateral) was used to indicate statistical significance.

3. Results

3.1. Comparison of clinical and imaging features (Table 1)

A total of 429 case (321 cases in the group without aneurysm and 108 cases in the group with aneurysm) with CAF were finally included. The CAF with aneurysm group included 56 males and 52 females with a mean age of 55.69 ± 12.93 years (range 18–80 years). The CAF without aneurysm group included 151 males and 170 females with a mean age of 54.98 ± 11.52 years (range 18–90 years). No significant differences in age, chest pain, chest tightness, palpitations, shortness of breath, dizziness, or ECG characteristics were observed between the two groups ($P > 0.05$). Meanwhile, significant differences in terms of heart murmur (10.19% vs 1.56%, $P < 0.001$) and infective endocarditis (IE) (10.19% vs 4.67%, $P = 0.038$) were observed between the two groups.

In terms of imaging features, there were no statistically significant differences between the two groups regarding fistulous origin and the number of fistulas ($P > 0.05$). At the same time, cases with coronary atherosclerosis, fistulous entry sites and diameter were statistically different in two groups ($P < 0.05$). The incidence of coronary atherosclerosis, large fistulous diameter and coronary-cardiac chamber arterial fistula was significantly greater in the CAF patients aneurysm than whose without. Reversely, the incidence of coronary-pulmonary artery fistula was less.

Table 2
Logistic regression analysis of clinical and imaging features.

	Univariate logistic regression analysis			Multivariate logistic regression analysis		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Coronary atherosclerosis	0.627	0.404–0.973	0.037*	0.488	0.280–0.851	0.012*
Drain into PA	0.443	0.242–0.810	0.008*	0.821	0.390–1.731	0.605
Drain into cardiac chamber	2.430	1.320–4.475	0.004*	4.013	1.602–10.051	0.003*
Fistulous diameter (cm)	1.242	1.107–1.394	< 0.001*	1.195	1.056–1.352	0.005*

PA, pulmonary artery; *$P < 0.05$ was used to indicate statistical significance.

3.2. Logistic regression analysis of risk factors for CAF with aneurysm (Table 2)

After conducting univariate logistic regression analysis, heart murmur, coronary atherosclerosis, IE, fistulous diameter and draining into PA, cardiac chamber and CS were related to CAF with aneurysm ($P < 0.05$) (Table 1). After removing the parameters with low incidence (cardiac murmur, IE, draining into CS), a multivariate logistic regression analysis was performed on the remaining parameters (Table 2). Ultimately, draining into the cardiac chamber [Fig. 1(A–C)] and large fistulous diameter [Fig. 2(A–C)] were the risk factors for CAF with aneurysm.

4. Discussion

Recently, the studies of CAF with or without aneurysms were shown to be helpful in the clinical management of CAF. According to clinical experience, small CAFs usually close spontaneously over time, so no special treatment is required. In contrast, medium or large fistulas tend to expand over time, significantly increasing the incidence of CAF-related symptoms and complications with age [6,7]. Moreover, larger fistulas are associated with higher morbidity of myocardial infarction [8]. Actually, the pathophysiology of CAF with aneurysms were commonly unknown, and no systemic treatment consensus was developed. However, Izumi et al. [9] showed that CAF with aneurysm is considered one of the most significant indications for surgery due to the potential risk of rupture. Batman et al. [10] have reported that among CAF patients with aneurysm diagnosed after undergoing percutaneous Transluminal Coronary had a higher 5-year mortality than those without aneurysm. Warisawa et al. [11] followed up on patients who underwent CCTA for risk assessment before non-cardiac surgery and found a high incidence (54%) of major adverse cardiovascular events in those with CAF complicating aneurysms. All these studies suggested that patients with symptomatic CAF should be treated. However, the surgical procedures for patients with CAF with or without aneurysms may differ [12,13]. Therefore, helpful information for developing appropriate patient management plans can be provided by an accurate and comprehensive assessment of the clinical and imaging features of CAF with or without aneurysms.

Compared with the clinical features between the CAF with aneurysm and CAF without aneurysm groups, the incidence of cardiac murmurs in the CAF with aneurysm group was significantly higher than CAF without aneurysm group (10.19% vs. 1.56%, $P < 0.001$). This result may be due to a larger fistulous diameter resulting in more blood shunts, and the diameter of the fistula in the CAF with aneurysm group is larger than the CAF without aneurysm group. The disturbance of blood flow caused turbulence and the formation of a turbulent field (vortex), which resulted in a greater probability of vibration of the blood vessel wall.

Coronary atherosclerosis is a chronic immunoinflammatory response triggered by damage to the intima of the blood vessels. Here, the incidence of coronary atherosclerosis in the CAF with aneurysm group was lower than that in the CAF without aneurysm group (42.59% vs. 54.21%, $P = 0.037$). This discovery differs from coronary artery aneurysms that are not located at the CAF fistula [14] and may be caused by changes in arterial blood flow. The blood flow of the coronary arteries occurs from the aorta with high pressure to the coronary sinus with low pressure. CAF can play a role in diverting blood, particularly when associated with aneurysms. Increased and stored blood flow within the aneurysm leads to reduced blood flow within the distal normal coronary artery. Reduced blood flow in the distal normal coronary arteries leads to reduced shear force in the coronary artery walls, which reduces the probability of intima injury and atherosclerosis.

The cause of CAF combined with aneurysm is currently unknown. Here, the incidence of IE was significantly higher in the CAF with aneurysm group than in the group without aneurysm (10.19% vs. 4.67%, $P = 0.007$). The damage to the vascular wall caused by IE leads to a significant decrease in the elastic tone of the muscle component of the vessel wall and a significant increase in vessel wall stress. This leads to vascular dilation and an increased probability of aneurysm formation [15]. Besides, congenital CAF is associated with the occurrence of IE, which can be the first clinical manifestation of CAF [16,17]. As such, IE may be both a result of CAF and an etiology of CAF complicated with aneurysm.

Compared with CAF with aneurysm, the diameter of fistula in the group without aneurysms was significantly smaller (3.51 ± 2.80 mm vs. 2.51 ± 1.70 mm, $P < 0.001$), and the risk of aneurysm may be increased by large fistulous diameter. This result may be due to

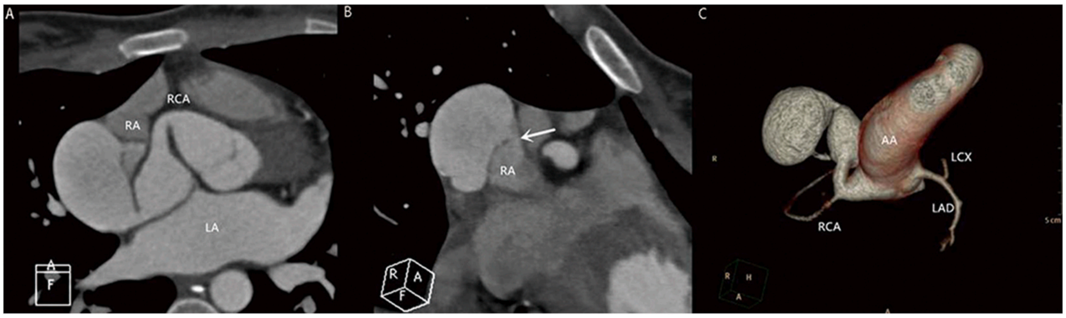

Fig. 1. Coronary artery-to-cardiac chamber fistula with aneurysm. An 18-year-old female had heart attack: A tortuous branch vessel originated from the RCA passes between the right atria and left atria (1A). Two aneurysmal-like ectasias (diameter of about 21.1 mm and 27.1 mm, respectively) are seen in this vessel, which eventually drains into the right atrium (arrow, 1B). The 3D image can clearly show the aneurysm of coronary artery-to-cardiac chamber fistula (1C).

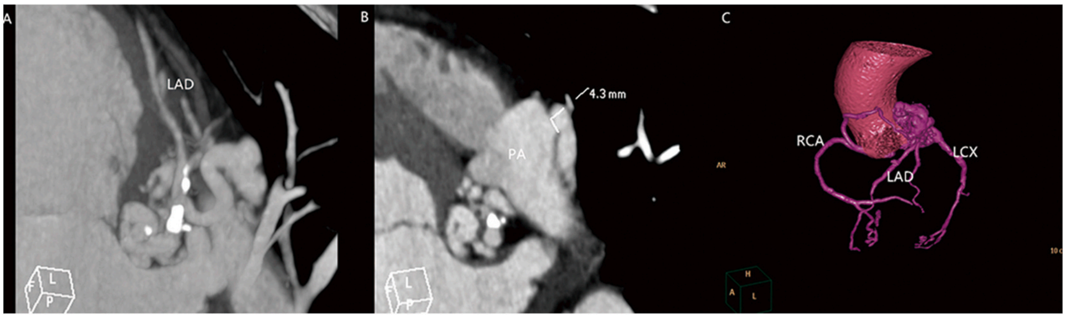

Fig. 2. Aneurysm with a large fistula. A 66-year-old female had chest and back pain for more than 20 days: A large intersecting and tortuous branch vessel with aneurysm-like ectasia (arrow 2A) originates from the LCA, and eventually drains into the PA. The fistula was approximately 4.3 mm in diameter (2B), and the 3D images show that the branch of sinuatrial node was involved (arrow 2C).

the formation of CAF aneurysms associated with sustained high blood flow in the coronary arteries [13,17]. High blood flow in the coronary arteries related to the size of the fistulous diameter in the CAF and the pressure difference between the coronary artery and the drainage region. A large CAF fistulous diameter may lead to high shunts as well as high coronary blood flow, resulting in a high likelihood of aneurysm. Hang et al. [18] have reported a similar conclusion that the average diameter of the fistula in the aneurysm group was significantly larger than that in the CAF without aneurysm group (2.99 ± 1.37 vs 2.54 ± 1.67). However, no significant difference was identified between the two groups in their study ($P = 0.499$), which may be due to the small sample size of patients in the two groups (n = 8 vs 14).

In this study, the entry site of CAF was associated with aneurysm, and CAF draining into cardiac chamber had an increased risk of aneurysm (OR, 4.013; 95%CI, 1.602–10.051). The formation of CAF aneurysms is associated with coronary dilation due to high blood flow in the coronary arteries. For coronary artery to cardiac chamber fistulas, the large pressure difference between the coronary artery and cardiac chamber results in relatively higher blood flow. Therefore, coronary-cardiac chamber arterial fistula has a high incidence of aneurysm and draining into cardiac chamber is a dependent risk factor for CAF complicated by aneurysm.

5. Limitations

We acknowledged that our study has several limitations. First, this study was retrospective, which may have led to a selection bias. Second, due to the large sample size, patients with CAF were not followed up and no longitudinal study data were available. Finally, the data from only one medical center, more center studies are needed.

6. Conclusion

Based upon the first large sample study of CAF, this research shows that larger fistulous diameter and coronary-cardiac chamber arterial fistulas are risk factors for CAF complicated by aneurysm. This result may contribute to more effective clinical management of CAF, especially those with aneurysms.

Production notes

This item belongs to the item group IG000035.

Author contribution statement

Li-Han Yang: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Ren-hui Cai: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Lu-Jing Wang: Performed the experiments; Analyzed and interpreted the data.
Li-Ping He: Contributed reagents, materials, analysis tools or data.
Xin-Xiang Zhao: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

The authors are unable or have chosen not to specify which data has been used.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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