



# Prevalence of coronary artery ectasia in older adults and the relationship with epicardial fat volume by cardiac computed tomography angiography

Jun-Jie Yang<sup>1\*</sup>, Xia Yang<sup>1\*</sup>, Zhi-Ye Chen<sup>2</sup>, Qi Wang<sup>1</sup>, Bai He<sup>1</sup>, Luo-Shan Du<sup>1</sup>, Yun-Dai Chen<sup>1</sup>

<sup>1</sup>Department of Cardiology, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China

<sup>2</sup>Department of Radiology, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China

## Abstract

**Objective** Coronary artery ectasia (CAE) refers to abnormal dilation of coronary artery segments to 1.5 times of adjacent normal ones. Epicardial fat is associated with cardiovascular risk factors. The relationship between CAE and epicardial fat has not yet been investigated. This study aimed to assess the relationship between CAE and epicardial fat volume (EFV) in older people by dual-source computed tomography coronary angiography (CTCA). **Methods** We prospectively enrolled 1400 older adults who were scheduled for dual-source CTCA. Under reconstruction protocols, patients with abnormal segments 1.5 times larger than the adjacent segments were accepted as CAE. EFV was measured by semi-automated software. Traditional risk factors in CAE patients, as well as the extent of EFV, were analyzed and compared to non-CAE group. **Results** A total of 885 male and 515 female older patients were enrolled. CAE was identified by univariable analysis in 131 patients and significantly correlated to hypertension, smoking, hyperlipidemia, prior percutaneous coronary intervention and ascending aorta aneurysm. EFV was shown to be significantly higher in CAE patients than patients without ectasia. In multivariable analyses, EFV ( $P = 0.018$ ), hypertension ( $P < 0.001$ ) and hyperlipidemia ( $P < 0.001$ ) were significantly correlated to CAE. There was a significant negative correlation between EFV and Markis classification. **Conclusions** CAE can be reliably recognized by dual-source CTCA. Epicardial fat might play a role in etiopathogenesis and progression of CAE, providing a new target for treating ectasia.

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**Keywords:** Coronary artery ectasia; Epicardial fat; Cardiac computed tomography angiography

## 1 Introduction

Coronary artery ectasia (CAE) has been observed and drawn clinical significance due to its unclear etiopathogenesis.<sup>[1]</sup> In spite of other pathological entities, atherosclerosis was cited as the main reason of CAE.<sup>[2]</sup> During coronary angiography, the incidence of CAE accounted for 1%-5% and has been reported to exceed 10% in patient with ischemic heart disease.<sup>[3]</sup> Computed tomography coronary angiography (CTCA) has emerged as a reliable image modality to detect coronary artery disease (CAD) of many types by an accurate description of vessel origin and course, particularly in anomalous vessels.<sup>[4]</sup> It can also provide a viable non-invasive imaging modality to elucidate potential coronary morphology of CAE, which can help reveal real incidence of CAE in patients with both symptoms and non-symptoms.

Certain risk factors resulting from media degeneration were found to be related to CAE, including adiponectin,<sup>[5]</sup> nitric oxide synthetase (NOS), matrix metalloproteinase-3 (MMP-3),<sup>[6]</sup> and so on. Some initial reports touched on the link between CAE and other coronary abnormalities, like coronary calcification.<sup>[7]</sup> Meanwhile, a number of recent studies have suggested an association between epicardial fat and coronary calcification.<sup>[8]</sup> There is a proportional relationship between the extent of coronary calcification and the amount of epicardial fat. Epicardial fat is also related to the extent of CAD and the risk of myocardial infarction.<sup>[9]</sup> Nevertheless, the correlation between CAE and epicardial fat volume has not yet been investigated. The aim of the present study, therefore, was to assess the prevalence and related characteristics of CAE and further delineate the relationship between CAE and epicardial fat in elderly people.

\*The first two authors contributed equally to this work.

**Correspondence to:** Yun-Dai Chen, MD, PhD, Department of Cardiology, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China.  
E-mail: cyundai301@sina.com

**Telephone:** +86-10-55499009

**Fax:** +86-10-55499009

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## 2 Methods

### 2.1 Study population

We prospectively enrolled 1400 consecutive older adults in stable condition who presented for diagnostic workup by cardiac computed tomography. Inclusion criteria were age >

60 years, clinically suspected CAD, and sinus rhythm, and written consent to participate in the study. The reasons for CTCA included atypical symptoms, typical angina and inconclusive stress test results, follow-up after PCI and Coronary artery bypass grafting (CABG). Information on traditional risk factors of each patient was obtained in a structured interview conducted by a physician.

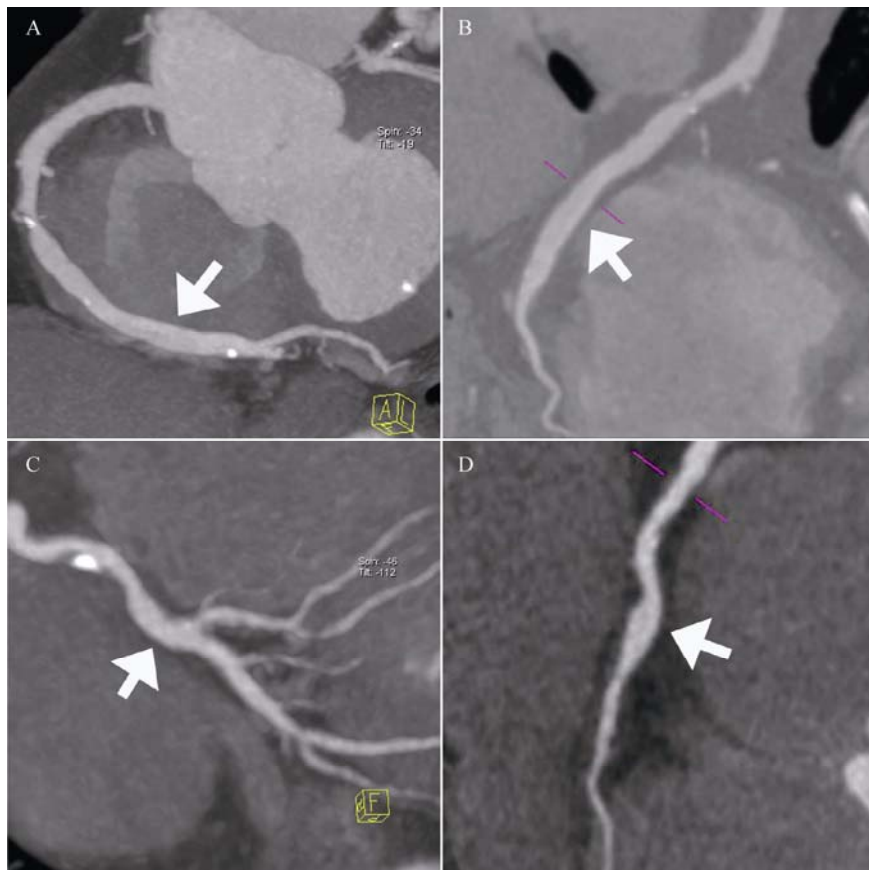
## 2.2 Dual-source CT protocol and image reconstruction

The patients were examined on a dual-source CT system (Somatom Definition Flash, Siemens Medical Solutions, Forchheim, Germany) with tube voltage 100 kV. Contrast media was injected, 60–80 mL (scaled to body weight) of Ultravist (370 mgI/mL, Shering AG, Guangzhou, China), or Omnipaque (350 mgI/mL, GE healthcare Limited, Shanghai, China), followed by a 40 mL saline bolus at the rate of 4.5–5.0 mL/s (scaled to venous condition) using a double-head injector (Medrad Stellant CT Injector System, Indianola, PA). Prospective electrocardiography (ECG) tube-current modulation was used at its maximum for

35%–75% of the R-R interval in all scans, triggered by the enhancement (100 HU) of the region of interest (ROI) in the ascending aorta with a delay of 10 s. The estimated radiation dose using this CTCA protocol was approximately 2–4 mSv.

## 2.3 Data analysis for CAE

Transverse-sectional reconstruction images in multiple planar reconstruction (MPR) were used to determine the diameter of coronary segments. CAE was defined as a coronary segment with a diameter of at least 1.5 times the diameter of the adjacent normal coronary artery in axial section. CAE was classified according to Markis classification.<sup>[10]</sup> The distribution of CAE was classified in each patient by two observers, in consensus, into four distinct types: type I, diffuse ectasia of two or three vessels; type II, diffuse disease in one vessel and localized disease in another vessel; type III, diffuse ectasia of one vessel only; and type IV, localized or segmental ectasia (Figure 1). Each segment was assessed for diameter, location, presence of atherosclerotic



**Figure 1. Characteristics of CAE in CTCA imaging.** Diffuse ectasia of right coronary artery was detected by both MIP and CPR images (A & B); MIP images (C) and CPR images (D) showed localized ectasia in a right coronary artery. The arrow in each image indicated the presence of ectatic lesion. CAE: coronary artery ectasia; CPR: curved multiplanar reconstruction; CTCA: computed tomography coronary angiography; MIP: maximum intensive projection.

changes (calcified and non-calcified) and concomitant coronary artery stenosis. An obstructive lesion was defined as severe luminal reduction ( $\geq 70\%$ ) compared with normal reference segment, while non-obstructive refers to mild and intermediate stenosis ( $< 70\%$ ). The ascending aorta was evaluated for the presence of aneurysms.

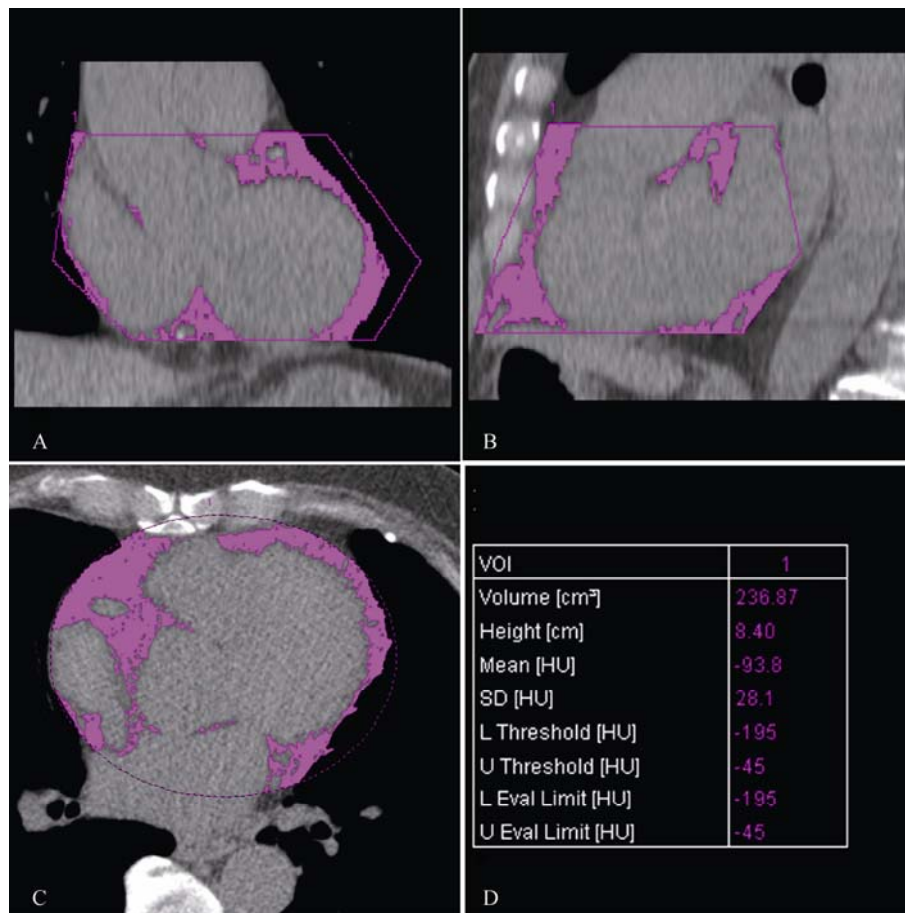
#### 2.4 Non-contrast CT measurement

Dedicated semi-automated software from Siemens support was used to quantify coronary calcium scans as well as epicardial fat volume (EFV). In the non-contrast CT data sets, all coronary calcium scans were reviewed by an expert reader using semi-automatic commercially available software to quantify coronary calcium. Total Agatston coronary artery calcium scores (CACS) was calculated as the sum of calcified plaque scores of all coronary arteries. The pericardium was automatically segmented using machine learning methods after estimating cardiac orientation and aligning a

heart model. Subsequently, the actual contours of the pericardium were locally detected to refine the final model and could be adjusted by the reader. As a result, a ROI delineating the pericardial sac was obtained. The fat content inside the ROI was then isolated with using a HU threshold, which was visually adjusted by the user to ensure that all fatty tissue within the pericardial sac could be included (Figure 2).

#### 2.5 Statistical analysis

Statistical analysis was performed by SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean  $\pm$  SD. Categorical data were presented as absolute frequencies (percentages). The quantitative values were compared using the two-sided Student's *t* test, and Chi-square test as categorical data. Spearman's Rho test was used to assess the relationship between epicardial fat volume and Markis classification. A value of  $P < 0.05$  was considered statistically significant.



**Figure 2. Measurement of the epicardial fat volume.** Both coronary and sagittal images are shown for determination of epicardial fat range (A & B). Using a lower threshold of -195 HU and upper threshold of -45 HU, epicardial fat is segmented and highlighted in red. The epicardial fat volume is summarized over all cross-sections (C) and in this coronary artery ectasia patient measured 236.87 mL (D).

### 3 Results

#### 3.1 Prevalence of CAE with CTCA

All the CTCA examinations were performed without adverse complication in our catheter lab. CAE were identified in 131 of the 1400 older adults (9.4%; 38 female, 93 male; median age: 71 years old; age range: 60-88 years). There were no other past medical histories which can be potential explanations for CAE, including Kawasaki disease, Takayasu arteritis and congenital CAD. The patients' characteristics for the CAE and non-CAE groups are presented in Table 1. There were statistically significant differences between the two groups with respect to hypertension, dyslipidemia, smoking habit and the presence of interventional characteristics (prior percutaneous coronary intervention), ( $P < 0.05$ ). As to CTCA-based diagnostic information, both the occurrence of ascending aorta aneurysm and the volume of epicardial fat were statistically higher in CAE group, but not for CACS scores. After estimated multivariable analysis, only EFV [Odds ratio (OR): 1.51, 95% confidence interval (95% CI): (1.13–1.99);  $P = 0.018$ ], hypertension [OR: 2.43, 95% CI (1.46–4.13);  $P < 0.001$ ] and hyperlipidemia [OR: 2.37, 95% CI (1.75–3.12);  $P < 0.001$ ] were significantly correlated to CAE.

**Table 1. General clinical parameters in the study groups.**

	CAE group (n = 131)	Non-CAE group (n = 1269)	P value
Age (yrs)	71.3 ± 8.6	69.9 ± 9.5	0.11
Male gender	93 (71.0%)	792 (62.4%)	0.05
BMI (Kg/m <sup>2</sup> )	27.3 ± 4.9	26.9 ± 6.1	0.47
Hypertension	88 (67.2%)	723 (57.0%)	0.000
Diabetes mellitus	93 (71.0%)	698 (55.0%)	0.63
Smokers	70 (53.4%)	562 (44.3%)	0.045
Dyslipidemia	82 (62.6%)	464 (36.6%)	0.000
Positive family history	26 (19.8%)	208 (16.4%)	0.31
Prior PCI	25 (19.1%)	157 (12.3%)	0.03
Prior CABG	6 (4.6%)	52 (4.1%)	0.79
Ascending aorta aneurysm	6 (4.6%)	21 (1.7%)	0.02
CACS score	212.6 ± 719.4	184.3 ± 842.6	0.71
Epicardial fat volume (mL)	139.6 ± 62.0	117.2 ± 88.5	0.005

Data are presented as n(%), or mean ± SD. BMI: body mass index; CABG: Coronary artery bypass grafting; CACS: coronary artery calcium score; PCI: percutaneous coronary intervention.

#### 3.2 Morphology of CAE in elderly patients

Evaluation of CTCA of the 131 elderly patients with CAE showed involvement of 414 segments in 254 coronary arteries (186 segments in the right coronary artery (RCA),

125 segments in the left anterior descending (LAD), and 103 segments in the left circumflex (LCX). CAE were most frequently found in the RCA (49.6%, 126/254), and less often in the left anterior descending (28.3%, 72/254) and circumflex artery (22.1%, 56/254).

With CTCA, only five patients (3.8%) had an isolated CAE with vessel enlargement, as the only pathological finding in otherwise normal coronary arteries. Just sixty nine patients (52.7%) with CAE had associated non-obstructive lesions ( $\leq 70\%$ ) in coronary segments, while 57 patients (43.5%) with CAE had significant obstructive lesions ( $> 70\%$ ). Table 2 shows the prevalence of patients with, or without, obstructive coronary lesions.

**Table 2. Prevalence of patients with coronary lesions.**

	CAE group	Non-CAE group	P value
Left main (n)	122	1225	--
Obstructive (%)	4 (3.3%)	32 (2.7%)	0.89
Non-obstructive (%)	27 (22.1%)	348(28.4%)	0.14
LAD (n)	131	1269	--
Obstructive (%)	43 (32.8%)	304 (24.0%)	0.02
Non-obstructive (%)	77 (58.8%)	804 (63.4%)	0.30
LCX (n)	130	1269	--
Obstructive (%)	39 (30.0%)	256(20.2%)	0.01
Non-obstructive (%)	58 (44.6%)	659 (51.9%)	0.11
RCA (n)	131	1268	--
Obstructive (%)	25 (19.1%)	335 (26.4%)	0.07
Non-obstructive (%)	79 (60.3%)	742(58.5%)	0.69

Due to anomalous origin and anatomy, the number of coronary arteries was not identical to the number of patients. Obstructive lesion was defined as severe luminal reduction ( $\geq 70\%$ ) compared with normal reference segment, while Non-obstructive refers to mild and intermediate stenosis ( $< 70\%$ ). CAE: coronary artery ectasia; LAD: left anterior descending; LCX: left circumflex; LM: left main; RCA: right coronary artery.

#### 3.3 Relationship with epicardial fat for CAE patients

According to the Markis classification, type I CAE was present in 10 (7.6%) patients, type II in 8 (6.2%), type III in 31 (23.6%), and type IV in 82 (62.6%), as were showed in Table 3. Through Spearman's Rho test, the value of Chi-square Tests for Linear-by-Linear Association was 29.114, suggesting that there was a negative correlation between EFV and Markis classification ( $r = -0.412$ ,  $P < 0.05$ ).

### 4 Discussion

CAE is a well-recognized angiographic finding, characterized by abnormal dilatation of the coronary arteries. In the present study, we aim to detect the incidence of CAE in older adults by CTCA. CAE is often viewed as a variant of

**Table 3. Relationship between CAE and EFV in elderly people.**

Type of CAE	All patients <i>n</i> = 131	Epicardial fat volume		
		Low ( $\leq 123$ mL)	Middle	High (> 182 mL)
Type 1	10	1	3	6
Type 2	8	2	2	4
Type 3	31	18	8	5
Type 4	82	62	14	6

CAE: coronary artery ectasia; EFV: Epicardial fat volume.

obstructive coronary atherosclerosis. Exaggerated positive vascular remodeling due to inflammation, and chronic overstimulation of the endothelium by nitric oxide are potential causative mechanisms.<sup>[11]</sup> In the general population, the condition is associated with cardiovascular risk factors, such as smoking and hypertension, while it appears to be inversely associated with age and diabetes mellitus (DM).<sup>[3]</sup> CAEs represent a common form of atherosclerotic CAD, seen in 5% of patients undergoing coronary angiography. Our study suggested that the incidence of CAE accounts for 9.4% in older adults. Limited diagnostic modalities may underestimate the real incidence of CAE in previous findings.<sup>[12]</sup> New non-invasive modalities like CTCA can reliably detect CAE based on contrast attenuation measurements which correlate well with the flow alterations assessed by coronary angiography.<sup>[13]</sup>

By comparison to the non-CAE group on baseline characteristics, there was a more statistically significant proportion of risk factors in CAE group, including hypertension, smoking and dyslipidemia, but not diabetes. A previous study defined male as predominant gender in CAE patients, with hypertension being the only risk factor showing increased prevalence in the general population.<sup>[14]</sup> Certain controversies exist on whether DM correlated with prevalence of CAE.<sup>[15]</sup> DM can induce negative remodeling in the arterial wall and thus impair compensatory arterial enlargement in the atherosclerotic process.<sup>[16]</sup> Therefore, it seems reasonable to consider an inverse correlation between CAE and DM. But other factors, such as insulin requirements and metabolic control, which were known to be correlated with DM, may tradeoff the effect of DM on vascular remodeling.<sup>[17]</sup> So, there is considerable complexity of the relationship between DM and progression of CAE. With respect to age level, the present study enrolled older adults with more severity of risk factors, suggesting that elderly CAE group represented occurrence of complicated clinical status. Our study also found that more patients with prior percutaneous coronary intervention and concomitant ascending aorta aneurysms were observed in older adults with CAE. It has been perceived that intervention to the coronary

arteries may result in formation of ectasia through vasculature positive remodeling,<sup>[18]</sup> especially in elderly populations for whom the inappropriate effects could accumulate in long time.<sup>[19,20]</sup> As a potential local presentation of systematic vascular ectasias, ascending aorta aneurysm usually accompanied the incidence of CAE.

CCTA can readily detect epicardial fat and coronary artery calcification with accuracy.<sup>[21]</sup> The current study evaluated other clinical parameters by useful coronary computed tomography based indicators, including CAC scores and epicardial fat volume. A previous study revealed a significant negative correlation between CACS and Markis classification for CAE.<sup>[22]</sup> However, there is no statistically difference between CAE group and non-CAE group for CACS in our study. This can be explained that older adults often represent higher calcification of vessels which can cause a bias of this kind. Through correlation analysis, pericardial fat was well associated with coronary artery calcification. Pericardial fat was increasingly recognized as an important mediator of metabolic risk, and also well associated with cardiovascular disease risk factors. Pericardial fat was also found to be correlated with higher triglycerides levels, lower high-density lipoprotein, hypertension, impaired fasting glucose, diabetes mellitus, and metabolic syndrome after multivariable adjustment.<sup>[23]</sup> To our knowledge, this is the first report on the relationship between CAE and pericardial fat in elderly population, although further details remain unknown.

In the present study, only less than 5% of CAE patients had no atherosclerotic lesions and more obstructive lesions (luminal reduction  $\geq 70\%$ ) could be found in CAE group. Actually, these data support CAE as a rare isolated finding by other researchers, with higher frequencies of co-existing atheromatous wall changes both in ectatic and non-ectatic segments.<sup>[24]</sup> Through our analysis, more obstructive lesions coexisted in the CAE group, especially for LAD and LCX. There is thus a trend towards which older adults with CAE are prone to be in a worse condition. Like most previous reports, the present study showed a higher incidence of CAE in the right coronary artery.<sup>[1]</sup> Although the reason for the higher predisposition of this coronary vessel to CAE is not well understood, it can be speculated that RCA is more easily affected by the nature of its long vascular route and even more pericardial fat alongside, which may be involved in the higher RCA predisposition to CAE.

There are certain limitations in this study. As a gold standard, invasive coronary angiography could not be used to verify the presence of CAE, even if the CTCA has become a reliable tool. Furthermore, laboratory tests concerning these diseases and their potential relationship with

epicardial fat could not be performed, and those should undoubtedly require further investigation.

In final analysis, older adults exhibit a higher incidence of CAE, which could reflect to some extent, the severity of atherosclerosis in this special population. As a result of complicated prepositions, there is a strong association between epicardial fat and CAE prevalence. With the new CTCA-based indicator, epicardial fat studies should be focused on evaluating, stratification and thus treating CAE in the elderly population.

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