ORIGINAL RESEARCH

Hakan Erkan MD¹
Mustafa T Ağaç MD¹
Seda Akyol MD²
Levent Korkmaz MD¹
Abdulkadir Kiriş MD¹
Merve Erkan MD³
Zeydin Acar MD¹
Bulent Vatan MD⁴
Emre Erkuş MD¹
Ali R Akyüz MD¹
Şükrü Çelik MD¹

¹ Department of Cardiology, Ahi Evren Cardiovascular and Thoracic Surgery Training and Research Hospital, Trabzon, Turkey

² Department of Radiology, Ahi Evren Cardiovascular and Thoracic Surgery Training and Research Hospital, Trabzon, Turkey

³ Department of Radiology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

⁴ Department of Cardiology, Sakarya Research and Training Hospital, Sakarya, Turkey

Coronary artery calcification score is increased in patients with isolated coronary artery ectasia

Abstract

Purpose: Coronary artery calcification (CAC) is an indicator of coronary atherosclerosis and is associated with future adverse cardiac events. Isolated coronary artery ectasia (CAE) is defined as localized or diffuse dilation of the coronary arteries without coronary stenosis. The aim of this study was to assess the relationship between CAC and isolated CAE.

Methods: Thirty-four patients with isolated CAE and 50 controls subjects, with normal coronary arteries, were enrolled in the study. Baseline demographic features and atherosclerosis risk factors were similar in both groups.

Results: Patients with CAE had higher total CAC than control subjects (84 ± 111 vs. 33.5 ± 103.5 ; $p < 0.001$). There was also a significant correlation between per-segment CAC and ectatic segment length ($r = 0.32$; $p = 0.01$) but no correlation with diameter ($r = 0.09$; $p = 0.5$).

Conclusion: Patients with isolated CAE had higher CAC than control subjects, suggesting that atherosclerosis may be involved in the pathogenesis of isolated CAE. Patients with isolated CAE may have increased cardiovascular risk and should receive appropriate risk stratification and relevant medical treatment.

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Correspondence to:

Hakan Erkan, M.D.

Ahi Evren Cardiovascular and Thoracic Surgery Training and Research Hospital,
Çamlık Street, 61040, Trabzon, Turkey

E-mail: drhakanerkan@hotmail.com

FIGURE 1. Panel A: Right coronary angiogram in LAO view in a patient with isolated coronary artery ectasia. Panel B: CT slice demonstrating coronary calcification of RCA (arrow) in the same patient; AO, aorta

Coronary artery ectasia (CAE) is defined as an enlargement of the vessel's lumen to greater than 1.5 times that of an adjacent normal artery or normal parts of the same vessel. Though etiologies causing CAE include congenital anomalies, inflammatory diseases and coronary interventions, in most cases it is atherosclerosis that plays the major role in the pathogenesis of CAE [1]. Isolated CAE, in which coronary artery stenosis, valvular heart disease and other cardiac disorders are not present, comprises only a small portion of the total CAE cases, with an incidence of 0.1–0.79% [2].

Coronary artery calcification (CAC) has long been known to occur as a part of the atherosclerotic process and the extent of the calcium deposition is thought to reflect the total coronary atherosclerotic burden [3]. There is scarce data about coronary artery calcification and ectasia. In this study, we aimed to assess the relation between CAC and isolated CAE.

Methods

Patient selection

Patients who underwent coronary angiography between May 2011 and June 2012 at our tertiary heart center because of typical anginal chest pain or documented ischemia, determined by non-invasive stress tests including exercise and myocardial scintigraphy, were consecutively enrolled in the study. Isolated CAE was defined as an enlargement of the vessel's lumen to

greater than 1.5 times that of an adjacent normal artery or normal parts of the same vessel in patients without coronary artery disease and/or other cardiac disorders (Figure 1). There were 34 patients with isolated coronary ectasia (Group 1). Fifty participants who had normal coronary arteries, and who were matched for age, gender and cardiovascular risk factors, were selected as a control group (Group 2). Exclusion criteria for both control and ectasia group were as follows: previous coronary artery disease or intervention, any visible stenotic coronary lesion, moderate to significant valvular disease, left ventricular dysfunction or wall motion abnormalities on echocardiography examination and any known inflammatory disease.

Assessment of coronary calcification

All patients in both groups were informed about the additional imaging modality and written consent was obtained for CT scans for the CAC measurements. Study protocol was approved by the hospital ethics committee. CT scans were performed by a 64-slice CT scanner (Toshiba, Aquillon 64, Toshiba Medical Systems, Otowara, Japan). The CT data was transferred to a remote workstation (Vitrea 2, Vital Images, Plymouth, Minnesota) and analyzed by two experienced observers. Calcium scores of each coronary artery and total CAC score (by summing scores of each artery) were calculated based on the Agatston method [4], where coronary calcification was

TABLE 1. Clinical and laboratory characteristics of patients with isolated coronary artery ectasia and control subjects.

	CAE (n= 34)	Control (n= 50)	P
Age, years	61 ± 8	59 ± 7	0.3
Male gender, n (%)	18 (53%)	27 (54%)	0.7
Hypertension, n (%)	24 (71%)	34(68%)	0.6
Diabetes mellitus, n (%)	9 (26%)	14 (27%)	0.8
Smoking, n (%)	13 (38%)	19 (39%)	0.5
Dyslipidemia, n (%)	16 (47%)	23 (45%)	0.7
Cholesterol-lowering drugs, n (%)	15 (44%)	22 (43%)	0.8
Systolic blood pressure (mmHg)	134 ± 15	131 ± 14	0.3
Diastolic blood pressure (mmHg)	70 ± 8	72 ± 9	0.4
CAC	84 ± 111.4	33.5 ± 103.5	<0.001
Total ectatic segments CAC	45.4 ± 76.6		
Total non-ectatic segments CAC	38.6 ± 58.2		
Number of ectatic arteries, n (%)			
One vessel	15 (44%)	-	
Two vessels	15 (44%)	-	
Three vessels	6 (12%)	-	
Total Cholesterol (mg/dl)	210 ± 30	214 ± 34	0.7
LDL-Cholesterol (mg/dl)	136 ± 26	137 ± 23	0.9
HDL -Cholesterol (mg/dl)	41 ± 6	44 ± 5	0.5
Triglycerides (mg/dl)	167 ± 28	163 ± 24	0.5

CAE: coronary artery ectasia; CAC : coronary artery calcification score; LDL : low-density lipoprotein; HDL: high-density lipoprotein.

defined as a lesion with an area greater than 1 mm² and a peak intensity greater than 130 HU.

Additionally, in patients with isolated coronary ectasia, 65 ectatic vessel segments were defined by conventional angiography and ectatic segment length and diameter were measured quantitatively with a dedicated conventional coronary angiography analysis program (Siemens Quantcor, Siemens Medical Solutions). Cardiac CT records for the corresponding segments (Figure 1) were examined for per-segment coronary calcification.

Statistical Analysis

Continuous variables were described as mean ± SD and analysed unpaired-t test and Mann-Whitney U test when appropriate. Chi-squared test was used for categorical variables. Analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. The correlation between coronary ectasia and clinical, angiographic characteristics was determined with Spearman and Pearson correlation

analysis. The Kruskal-Wallis test was used to compare CAC in patients with one, two and three diseased vessels. A p-value of <0.05 was considered statistically significant.

Results

Baseline laboratory and clinical characteristics of patients and control group are summarized in Table1. There was no statistically significant difference between the groups in terms of gender, age, cardiovascular risk profile and cardiovascular medical therapy (Table 1). Ectasia involved the left anterior descending artery in 19 (56%), the left circumflex artery in 16 (48%), and the right coronary artery in 22 (64%) patients. One vessel, two vessels and three vessels ectasia were found to be present in 15 (44%), 15 (44%) and 4 (12%) patients, respectively (Table1). Patients with CAE had higher total CAC than control (84 ± 111 vs. 33.5 ± 103.5; <0.001). On the other hand, there was no statistically significant differences in total CAC in patients with CAE of one vessel, two vessels or three vessels, although a trend for an increase in CAC was observed (62 ± 93; 93 ± 104

and 120 ± 168 , respectively $p=0.52$). Ectatic and nonectatic segments of CAC were also calculated in Group 1. Ectatic segments had higher calcium score than non-ectatic segments (45.4 ± 76.6 vs. 38.6 ± 58.2). Mean ectatic segment length and diameter were 35 ± 17 and 5.0 ± 0.9 mm, respectively. There was a statistically significant correlation between per-segment CAC and ectatic segment length ($r=0.32$, $p=0.01$) but no correlation with ectatic segment diameter ($r=0.09$; $p=0.5$).

Discussion

In the present study, increased CAC was found in patients with CAE compared with the control group. A significant correlation was found between per-segment CAC and ectatic segment length, but not with ectatic segment diameter. There was a trend for an increase in total CAC, as was seen with the increase in number of ectatic coronary arteries, which did not reach statistical significance - probably due to the limited sample size.

Atherosclerosis starts insidiously in adolescence, as fatty streaks composed of macrophage white blood cells, and progresses over the ensuing years into preatheromas, atheromas, fibroatheromas and complicated lesions. Subintimal coronary calcification forms as a result of instability and rupture of an atheromatous lesion, thus leading to deposition of calcification during healing phase. [5-6]. During this time period, it is thought that there is a change in plaque characteristics from noncalcified lesions to mixed and subsequently calcified plaques.

The presence of calcium in coronary arteries is pathognomonic of atherosclerosis [7]. The close correlation between the atherosclerotic plaque burden and the extent of CAC has been confirmed both by histopathology and intravascular ultrasound [8-9]. CAC has been proposed as a useful imaging marker for atherosclerotic burden and risk of future cardiovascular events [10].

The coexistence of coronary ectasia with coronary atherosclerosis raised the concept that ectasia may represent a variant of coronary artery disease [11]. Celik *et al.* demonstrated significant correlation between isolated CAE and carotid intima media thickness, which is a well known surrogate marker of atherosclerosis [12]. An increased level of lipoprotein-associated phospholipase A2 (Lp-PLA2), an inflammatory marker that potentiates intravascular inflammation and atherosclerosis, has been reported in patients with isolated CAE [13]. Aksu *et al.* proposed that patients who have isolated CAE or CAE with CAD have similar etiopathogenesis as they have considerably similar risk factors [14]. On the other hand, both types of CAE (isolated CAE and CAE with coronary stenosis)

may lead to similar clinical presentation and prognosis; for example, Zografos *et al.* have recently shown that it is the extent of CAE that is most the important factor in coronary flow and clinical picture rather than the type of CAE [15]

Calcification is a natural phenomenon occurring in most atherosclerotic plaques and is typically limited to the subintimal space. Therefore, CAC score has emerged an indicator of coronary atherosclerosis and as a potential marker of risk of cardiovascular events. The extent of coronary atherosclerosis, rather than the severity of stenosis, is the most important predictor of death due to acute MI or sudden cardiac death [16]. Similarly, the prognosis of CAD is more closely related to the atherosclerosis plaque burden and stability than the extent of a particular stenosis [17]. This study was designed to investigate the potential CAC score as an indicator of atherosclerosis in patients with isolated CAE. CAC scores in patients with isolated CAE were increased compared with controls and a significant relationship was found between CAC score and ectatic segment length but not with ectatic vessel diameter. While atherosclerosis is the key pathogenic mechanism for CAE, not all vessels afflicted by atherosclerosis show significant dilatation. Therefore, other mechanisms may play a role in phenotypic diversity of atherosclerotic vessel dilatation. It was previously hypothesized that high intraluminal coronary pressures, as seen in episodic and systemic hypertensive states, may contribute to aneurysm formation [18-19]. Those unresolved contributing mechanisms may explain why we could not find any significant association between ectatic vessel diameter and CAC.

Only one previous study evaluated the relationship between CAE and coronary calcification. Farrag *et al.* reported a paper which investigated the prevalence of CAE and its relationship with coronary artery calcification in a large diversity of population [20]. They compared CAC scores of patients with CAE who had obstructive (defined by $\geq 70\%$ luminal narrowing) and non-obstructive coronary stenosis and found that patients with CAE had higher CAC scores than those without CAE. In addition, they showed that the prevalence of non-obstructive coronary lesions was higher in patients with CAE than those without CAE. In contrast to our study, the relationship between isolated CAE and CAC score was not specifically investigated (only 16% of all CAE cases were the isolated form) and any specific data was not reported in their study. Moreover, they evaluated coronary arteries with CT coronary angiography and only few patients underwent conventional coronary angiography. This situation may limit the applicability of their results. Hoffmann *et al.* reported that high attenuation structures, such as heavy calcification, may obscure coronary adja-

cent tissue, limiting the accuracy of CT significantly [21]. In addition, recently released 2010 appropriate use criteria for cardiac computed tomography regards the usefulness of coronary CT angiography as uncertain at Agatston scores more than 400 [22]. In contrast, the present study consisted only of patients with isolated CAE who had no visible coronary stenosis and all patients in the study population underwent conventional coronary angiography. Therefore, our study differs from Farrag's studies and our results may better reflect the relationship between CAE and CAC score in patients with isolated CAE.

In summary, the results of our study suggest that patients with isolated CAE have a great atherosclerotic burden indicated by higher CAC scores. Secondly, the atherosclerotic pathway plays a major role in the pathogenesis of CAE. Finally, based on higher CAC scores, the possibility of future cardiovascular events may be higher in patients with isolated CAE.

Study limitation

The most important limitation of the present study is its small sample size; and to limit the effects of this small sample size, patient selection was made very carefully. Patients with any visible coronary stenosis or with cardiac or extra-cardiac disease, which may potentially predispose CAE, were excluded from the study. In this way, we attempted to obtain a small but reliable study population. Although the subjects were defined as having normal coronary arteries, based on coronary angiography, we could not rule out reliably whether these patients were free of atherosclerosis – to do so would have required additional imaging such as intravascular ultrasound.

Conclusion

Increased CAC was demonstrated in patients with isolated CAE. Considering that increased CAC reflects atherosclerotic burden, which has a prognostic impact, patients with isolated CAE, who may have increased cardiovascular risk, require appropriate risk stratification and intensive treatment.

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