Comparison of Outcomes of Diseased Coronary Arteries Ectasia, Stenosis and Combined

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Background: Coronary artery ectasia (CAE) is a localized or diffuse abnormal dilatation of coronary arteries. Controversy still remains about its cardiovascular events rate, prognosis, and etiology. Adverse effects of CAE coinciding with coronary artery stenosis (CAS) (and in isolated form) are unclear.

Objectives: We aimed to investigate the cardiovascular event rate of CAE in comparison to 'CAS only', and comparing their etiology.

Patients and Methods: This cross-sectional study was conducted on 200 patients between May 2011 and June 2012. Of them, 40 had CAE (case group) and 160 had only CAS (control group). Patients with CAE were divided into 2 subgroups according to the absence (E_1) or presence (E_2) of CAS. They were followed up for at least 6 month for cardiovascular events, including death, unstable angina and myocardial infarction (MI). Finally, we compared findings in CAE, CAS, and E_1 and E_2 subgroups and evaluated the relationship between severity of ectasia (1-1.5 times, 1.5-2 times, and > 2 times) and CAS.

Results: Hypertension (HTN), dyslipidemia (DLP), and male sex were matched in both groups without significant difference. Cigarette smoking (C/S) was significantly higher and diabetes mellitus (DM) was significantly lower in CAE compared to CAS patients. A subgroup of CAE patients with CAS (E_2 subgroup) had significantly higher mortality rate than isolated CAS (P = 0.043). MI was seen in several isolated CAE patients (E_1) subgroup. Severity of ectasia showed no significant relationship with CAS.

Conclusions: Presence of CAE in patients with CAS increases its cardiovascular event rate. Isolated CAE is not a benign finding and MI can occur. Risk factors of CAE are similar to CAS, but C/S is more associated with CAE than CAS. DM is seen in CAE patients less than CAS.

Keywords: Coronary Stenosis; Risk Factor; Prognosis

1. Background

Coronary artery ectasia (CAE) is a localized or diffuse abnormal dilatation of epicardial coronary arteries. It has been defined as a condition in which diameter of coronary arteries exceed the normal adjacent segment or the largest normal coronary vessel (1). According to coronary artery surgery study (CASS) registry, coronary artery ectasia is defined as dilatation of coronary arteries to a diameter of more than 1.5 times of its normal adjacent segment (2). The incidence of this abnormality is between 0.3%-5% (related to study population). It is more prevalent in Asia and South Europe and less prevalent in North Europe. CAE mostly affects right coronary artery (2, 3).

Different possible etiologies are proposed for CAE, including atherosclerosis, Kawasaki disease, Takayasu, congenital disorders, post-stenting (iatrogenic), polyarteritis nodosa, syphilis, polycystic kidney disease, and familial homozygous hypercholesterolemia (4-6). Higher levels of local metalloproteinase and plasma soluble adhesion molecules such as ICAM-1, VCAM-1, and E-selectin are also observed in CAE patients (7, 8). Moreover, varicose veins and varicocele are significantly higher in this condition, which may suggest the possible existence of a generalized defect in the vascular wall (9). In this regard, Guy et al. showed increased prevalence of CAE in patients with abdominal aortic aneurysms (10). Most risk factors of CAE are similar to coronary artery stenosis (CAS), including cigarette smoking, male gender, hypertension (HTN), positive family history of coronary artery disease, elevated CRP and hyperhomocysteinemia (2, 11-13). Interestingly, diabetes mellitus (DM) is significantly lower in CAE patients in comparison to CAS group (11, 14).

Prevalence of cardiovascular events and prognosis of CAE has not yet been clearly determined and remains controversial. Some studies showed increased cardiovascular events such as unstable angina, MI, heart failure (HF), sudden cardiac death (SCD), and angina in 'CAE only' patients. These studies have also reported poor prognosis for 'CAE only' in patients with CAS and 3 vessels disease (15-17). Furthermore, the coexistence of CAE with coronary artery stenosis augments cardiovascular

events (16). In the literature, different CAE mortality rate is reported such as biannually 15% (16), triennially 13% (18) and annually 1.5% in medically treated patients (19). Thus, accurate rate of mortality is not delineated yet. However, some studies reported relatively better prognosis for CAE. Demopoulos et al. reported good prognosis for isolated CAE despite history of previous MI (18). In the CASS study, no survival difference reported between patients with or without CAE (2). Sadr Ameli and Sharifi showed no difference in MI or mortality rate at 2-year follow-up between patients with or without CAE (19), and Hartnell et al. reported that CAE did not alter patients' outcome (20).

2. Objectives

This study was performed because of controversial results in the previous studies and lack of conclusive data about prognosis, cardiovascular events, and risk factors of CAE.

3. Patients and Methods

This prospective cross-sectional study was done on consented patients undergoing elective or urgent angiography with confirmed CAE or CAS, in Rajaie Cardiovascular, Medical and Research Center, a large tertiary heart center in Iran between May 2011 and June 2012. This study was approved in local Ethics Committee. After conventional angiography, consecutive patients with CAE (40 patients) and 'CAS only' (160 patients) were enrolled in the study. To improve the study power, the number of CAS patients was 4 times more than the patients with CAE. The exclusion criteria were severe valvular disease, cardiomyopathy, aortic dissection, intracardiac shunts, coagulopathy, vasculitis, connective tissue disease, and patient's incorporation. Demographics data included age, sex, history of MI, DM, HTN, dyslipidemia, and cigarette smoking (C/S) were recorded and patients were evaluated for aneurysm of ascending aorta and LV systolic function. CAE patients according to the absence or presence of concomitant CAS were divided into E_1 and E_2 subgroups.

There was no consensus in reference to vessel definition but we used local ectasia, so dilation of more than 1.2 mm was our reference point.

In addition, patients with CAE were divided into 3 subgroups regarding the severity of ectasia (CAE 1.2-1.5 times, 1.5-2 times, and more than 2 times of the largest normal adjacent artery). Ectatic vessel diameter and ratio of ectatic segment to normal segment diameter were determined using QCA system. CAS was defined as stenosis equal or more than 70% of vessels diameter which measured with visual assessment. Evaluation of left ventricular (LV) systolic function and root of ascending aorta were done with transthoracic echocardiography (TTE) and dilatation of aortic root was defined as a diameter more than 38 mm at sinus of Valsalva level.

Finally, all patients followed up for cardiovascular events (including MI, unstable angina, and cardiac death) during a six-month period. The statistical analysis was performed by SPSS 15. The descriptive data were presented as mean and standard deviation (SD) for the interval variables and frequency (%) for the categorical variables. The Student t-test, Spearman, chi-square or Fisher exact test was used to compare the results between the study groups. Multiple linear and logistic regression models were applied to investigate the adjusted associations between variables. P < 0.05 was considered significant. Medical treatment was prescribed for both groups, which were matched regarding their treatment.

4. Results

A total of 200 patients, including 40 CAE and 160 CAS only patients were enrolled in the study. All patients with CAE were followed successfully (without loss), but seven patients with CAS dropped out of the study (loss to follow up = 4%), which was statistically insignificant. Male sex (P = 0.024), cigarette smoking (P = 0.04) were significantly higher in patients with CAE compared to patients with CAS. On the other hand, DM was significantly higher in patients with CAS compared to patients with CAE (P = 0.001) (Table 1). Mortality rate in E_2 subgroup (7.3 % (n = 2)) were significantly more than patients with CAS only (1.3% (n = 2)) (P = 0.043). Other cardiovascular events, including MI and unstable angina were equal between these two groups without statistically significant difference (Table 2). The study showed no significant difference regarding cardiovascular events, including unstable angina (P = 0.08), cardiac death (P = 0.14) and MI (P = 0.37) between patients with CAE and patients with CAS only (Table 3). Our results also showed no significant difference between CAE and CAS only patients in some variables, including age (P = 0.06), dyslipidemia (P = 0.38), HTN (P = 0.61), history of MI (P = 0.12), LV systolic function (P = 0.39) (Table 4). We found that severe ectasia (ectasia > 2 times larger than normal adjacent artery) is more prevalent in right coronary artery (RCA) (43%) and mild ectasia (ectasia 1-1.5 times larger than normal adjacent artery) is more prevalent in left anterior descending artery (LAD) (43%). Moreover, ectasia dominantly occurs in proximal (45%) and then mid portion (42%) of coronary arteries. CAE patients with ectasia > 2 times of normal adjacent arteries in comparison to ectasia 1-2 times had no significant difference in view of cardiovascular events, risk factors, and history of MI (Table 5). The analysis showed no significant relationship between severity of ectasia and CAS (Table 6). On admission of E_1 patients, 4 had clinical findings in favor of MI (28.6%) (Table 7). Dilatation of aortic root was not seen in patients with CAE. Except history of previous MI which was significantly higher in E_2 than E_1 subgroup of CAE patients, we found no significant difference in cardiovascular events and risk factors between two subgroups of CAE (Table 7).

Table 1. Frequency of Variables in Ectasia (E_1 and E_2) and in CAS Only Patients [a, b]

	CAS Only	Ectasia	P value
DM	69 (43)	5 (12.5)	0.00
HTN	75 (46)	17 (42)	0.61
CS	45 (28)	18 (45)	0.04
DLP	64 (40)	19 (47.5)	0.38
History of MI	50 (32.5)	8 (20)	0.12
MI at admission	50 (33.6)	18 (46.2)	0.14
Male	102 (63)	33 (82)	0.024
Aortic root aneurysm	2 (1.3)	0 (0)	0.47

[a] Abbreviations: CS, cigarette smoking; DM, diabetes mellitus; DLP, dyslipidemia; HTN, hypertension.
[b] Data are presented as No. (%).

Table 2. Comparison of E_2 Subgroup of Coronary Artery Ectasia with Coronary Artery Stenosis Only Patients [a, b]

	E_2 Subgroup of CAE	CAS Only	P value
DM	3 (11.5)	69 (43.1)	0.002
HTN	9 (34.6)	75 (46.9)	0.24
C/S	13 (50)	45 (28.1)	0.02
DLP	13 (50)	64 (40)	0.33
Age, y	58.2 (11)	60.3 (9.95)	0.31
Sex, Male	21 (80.8)	102 (63.8)	0.08
History of MI	8 (30.8)	50 (32.5)	0.86
MI at admission	14 (56)	50 (32.5)	0.03
Death	2 (7.7)	2 (1.3)	0.043
Unstable Angina	0 (0)	11 (7.2)	0.15
MI	0 (0)	3 (2)	0.47

[a] Abbreviations: CAE, coronary artery ectasia; DM, diabetes mellitus; HTN, hypertension; C/S, cigarette smoking; DLP, dyslipidemia; MI, myocardial infarction.
[b] Data are presented as No. (%).

Table 3. Frequency of Cardiovascular Events in Ectasia (E_1 and E_2) and in Coronary Artery Stenosis Only Patients During 6 Month Follows up [a, b]

	CAS Only	Ectasia	P value
Death	2 (1.3)	2 (5)	0.14
Myocardial infarction	3 (2)	0 (0)	0.37
Unstable angina	11 (7.2)	0 (0)	0.08

[a] Abbreviations: CAS, coronary artery stenosis.
[b] Data are presented as No. (%).

Table 4. Comparison of Age and Left Ventricular Systolic Function in Coronary Artery Stenosis (E_1 and E_2) and in 'CAS Only' Patients [a, b]

	CAS Only	Ectasia	P Value
Ejection Fraction, %	43 ± 11.2	45 ± 8.4	0.39
Age, y	60 ± 9.9	57 ± 10.3	0.06

[a] Abbreviations: CAS, coronary artery stenosis.
[b] Data are presented as Mean ± SD.

Table 5. Frequency of Variables in Patient With Ectasia ≥ 2 Times and Patients With Ectasia < 2 Times [a, b]

	Ectasia ≥ 2 times	Ectasia < 2times	P value
DM	2 (15.4)	3 (11.1)	0.70
HTN	5 (38.5)	12 (44.4)	0.72
CS	7 (53.8)	11 (40.7)	0.43
DLP	7 (53.8)	12 (44.4)	0.57
History of MI	3 (23.1)	5 (18.5)	0.73
MI at admission	7 (58.3)	11 (40.7)	0.30
Male sex	10 (76.9)	23 (85.2)	0.51

[a] Abbreviations: CS, cigarette smoking; DLP, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction.
[b] Data are presented as No. (%).

Table 6. Prevalence of Coronary Artery Stenosis in Different Size of Ectasia [a, b]

	Absence of CAS	Presence of CAS	P Value
Ectasia 1-1.5 times	9 (31)	20 (69)	0.39
Ectasia 1.5-2 times	7 (29.2)	17 (70.8)	0.34
Ectasia > 2 times	4 (30.8)	9 (69.2)	0.69

[a] Abbreviations: CAS, coronary artery stenosis.
[b] Data are presented as No. (%).

Table 7. Comparison E_1 and E_2 Subgroups of CAE Patients [a, b]

	CAE		P value
	E_1 (CAE Without CAS)	E_2 (CAE With CAS)	
Total number	14 (35)	26 (65)	
Male	12 (85.7)	21 (80.8)	0.69
DM	2 (14.3)	3 (60)	0.8
HTN	8 (57.1)	9 (34.6)	0.16
DLP	6 (42.9)	13 (50)	0.66
C/S	5 (35.7)	13 (50)	0.38
History of MI	0 (0)	8 (30.8)	0.020
MI at admission	4 (28.6)	14 (56)	0.09
Cardiac death	0 (0)	2 (7.7)	0.28
Unstable Angina	0 (0)	0 (0)	0
MI in follow up	0 (0)	0 (0)	0

[a] Abbreviations: CAS, coronary artery stenosis; CAE, coronary artery ectasia; CS, Cigarette Smoking; DM, Diabetes Mellitus; DLP, Dyslipidemia; HTN, Hypertension; MI, Myocardial Infarction.
[b] Data are presented as No. (%).

5. Discussion

This study showed a higher mortality rate in E_2 subgroup of CAE patients in comparison to 'CAS only' group. Our result also showed that mortality and history of previous MI were significantly higher in E_2 than E_1 subgroup. This increased rate of mortality and previous MI is compatible with results of some previous studies, which showed adverse outcomes and increased mortality in CAE accompanying CAS (16). However, some other studies demonstrated relatively benign and good prognosis for CAE, which are in contrast with our results (2, 3, 18, 19).

After six months follow up, none of our CAE patients had unstable angina or MI, but 18 patients (45%) (including 4 patients from E_1 subgroup) had MI at admission time and 8 patients (20%) had history of previous MI. These results indicate that although we could not find unstable angina or MI in our relatively short follow up period in CAE pa-

tients, these complications are frequently seen in both subgroups of CAE (E_1 and E_2). This shows that isolated CAE is not a benign finding. Furthermore, mortality rate was not significantly different between CAE and 'CAS only' patients (P = 0.14), which shows CAE patients has poor outcome like CAS patients (Table 3). However, mortality in CAE patients is only associated with E_2 subgroup.

In this study, atherosclerosis risk factors, including HTN and dyslipidemia were seen in both CAE and 'CAS only' patients without significant difference (P = 0.61) (P = 0.38), but C/S is significantly higher in CAE compared to 'CAS only' patients (P = 0.04). It may indicate that HTN, dyslipidemia, and mainly C/S are important risk factors for CAE. One of the important finding of the present study is that DM were significantly lower in CAE than 'CAS only' patients (P = 0.001), which is in agreement with recently published articles (11, 14). It seems that DM has an important role in decreasing rate of CAE. Further studies are needed to assess how DM can alter development of CAE. We found no dilatation of aortic root in patients with CAE (0%). It seems that CAE has no relationship with the aneurysm of aortic root. CAE patients with ectasia > 2 times of normal adjacent arteries in comparison to ectasia 1-2 times had no significant difference in view of cardiovascular events, risk factors and history of MI (Table 5). These findings may reveal that severity of ectasia has no adverse effect on prognosis and outcome. We found that severity of ectasia had no significant relationship with CAS (Table 6), and CAS can be seen with CAE regardless of its severity. In line with previous reports (2, 3), in this study severe ectasia (ectasia > 2 times) was dominantly observed in RCA, but mild form of ectasia was mostly found in LAD. It is not clear why RCA is more susceptible to severe form of ectasia, which needs to be clearly determined.

Our present study had some limitations; most importantly its relatively small sample size of CAE patients and then its short follow-up duration. E_2 subgroup of CAE patients had significantly more cardiovascular events than 'CAS only' or E_1 subgroup. It seems that CAE concomitant with CAS has poor outcome and needs more aggressive treatments. Since MI was seen in some members of E_1 subgroup, isolated CAE is not a benign finding and may need therapeutic approach like CAS. Also, severity of ectasia had no significant relationship with CAS. Further studies with larger population and longer follow up periods are required to confirm these findings.

Acknowledgements

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