Characteristics of coronary artery ectasia and its association with carotid intima-media thickness and high sensitivity C-reactive protein

Osama Sanad¹, Eman Al-Keshk², Ahmed Ramzy³, Mohammed A. Tabl⁴, Ahmed Bendary⁵

¹,²,³,⁴,⁵ Cardiology department, Benha university hospital, Benha faculty of medicine, Egypt.

This study was conducted to uncover the relation between coronary artery ectasia (CAE) and markers of atherosclerosis. A total of 1611 coronary angiograms were prospectively examined to find out patients with CAE. Those patients were divided into 2 groups: Mixed CAE with stenotic coronary artery disease (CAD) “group 1” and pure CAE “group 2”. Two control groups of age-adjusted subjects were selected consecutively in a 1:1 fashion; one with normal coronaries “group 3” (Pure CAE: normal coronaries) and the other with obstructive CAD only “group 4” (Mixed CAE: obstructive CAD). All recruited subjects underwent carotid intima-media thickness (IMT) and high sensitivity C-reactive protein (hs-CRP) level measurements. Out of examined angiograms, 35 subjects showed mixed CAE “group 1” and 26 showed pure CAE “group 2”. Age and gender-adjusted logistic regression analysis model revealed that significant independent predictors for CAE were: hypertension, smoking, absence of DM and hs-CRP level > 3 mg/L. Mean carotid IMT was significantly higher in group 2 than group 3 and in group 4 than group 1 (1±0.1 versus 0.4±0.2 mm and 1.4±0.4 versus 1±0.2 mm respectively, P < 0.001 for both). Mean hs-CRP level was significantly higher in group 1 than group 4 and in group 2 than group 3 (7±2 versus 3±0.8 mg/L and 6±2 versus 1±0.6 mg/L respectively, P < 0.001 for both). We concluded that atherosclerosis may not be the only plausible explanation for CAE.

Keywords: Coronary artery ectasia; Carotid intima-media thickness; high sensitivity C-reactive protein; Atherosclerosis.

INTRODUCTION

Coronary artery ectasia (CAE), sometimes known as ‘dilated coronopathy’, is relatively uncommon angiographic finding (Lam and Ho, 2004). This condition is diagnosed if the diameter of a dilated segment of an artery is 1.5 times greater than the diameter of the adjacent normal segments of the artery (Hartnell et al, 1985). Markis et al, 1976 introduced the following classification of CAE based on the extent of coronary affection: type I, diffuse ectasia of two or three vessels; type II, diffuse disease in one vessel and localized disease in another one; type III, diffuse ectasia of one vessel only; and type IV, localized or segmental ectasia. Coronary angiography remains the main diagnostic tool for CAE (Mavrogeni, 2010). The clinical presentation and the long-term cardiac complications have long been thought to be associated with the severity of the co-existing obstructive coronary lesion, despite the fact that ‘pure’ coronary ectasia (without obstructive coronary lesions) can be implicated in angina or myocardial infarction (Demopoulos et al, 1997).
Regardless of the severity and extent of CAE, the etiology, prognosis, morbidity, and mortality related to this pathology are still a matter of debate and whether CAE is a unique clinical finding or a state resulting from other entities is still unknown (Amirzadegan et al, 2014). Despite the fact that about 50% of cases are due to atherosclerosis and histopathological examination of ectatic segments has revealed mainly destruction of the media layer of the artery (Yetkin et al, 2005). It’s still not clear which additional factors promote the development of ectasia in these patients (Cohen and O’Gara, 2008). Carotid artery intima–media thickness (IMT) is widely used as a surrogate marker for atherosclerotic disease. Carotid IMT measured by ultrasonography has been shown to be correlated with coronary artery disease as defined by angiography (Çelik et al, 2007). Hs-CRP level is gaining acceptance now as an on-the-horizon marker for possible inflammatory pathophysiologic origin of atherosclerotic vascular disease (Ozbay et al, 2006). Therefore, studying carotid IMT and hs-CRP in those patients could give insights into pathogenic mechanisms of CAE.

**PATIENTS AND METHODS**

**Study design**

This is a single center, prospective observational case-control study that included selection of cases proved to have CAE through consecutive examination of coronary angiograms done at the catheterization laboratory at Benha University Hospital over a period of 18 months (from September 2014 to February 2016). We aimed primarily to study clinical and angiographic characteristics of CAE patients in addition to studying the association between it and both carotid intima-media thickness and hs-CRP levels as surrogate markers for atherosclerotic disease. Cases proved to have CAE were divided into 2 groups: mixed CAE with obstructive CAD “group 1” and pure CAE “group 2”. Two control groups were included for comparisons: a group of age-adjusted subjects with normal coronary angiograms, selected consecutively in a 1:1 fashion (Pure CAE: normal coronaries) “group 3” and another group of age-adjusted subjects with obstructive CAD without ectasia selected consecutively in a 1:1 fashion (Mixed CAE: obstructive CAD) “group 4”. Patients with CAE associated with cardiomyopathies, valvular and congenital heart diseases were excluded to make sure that all patients are being evaluated exclusively for possible CAD. Patients with iatrogenic CAE due to previous coronary interventions (either percutaneous coronary intervention ‘PCI’ or coronary artery bypass graft ‘CABG’) were also excluded. The study was approved by the local ethics committee at our institution and an informed consent was obtained from each participant.

**Coronary angiogram analysis**

Coronary angiograms done in the defined study period were prospectively analyzed by experienced cardiologists (two for each angiogram) at Benha University Hospital to find out those patients with CAE. CAE was defined according to the landmark Coronary Artery Surgery Study (CASS) as a dilatation of coronary artery ≥ 1.5 times in diameter when compared to the adjacent normal segment, with localized ectasia defined as < 1 cm in length and diffuse ectasia ≥ 1 cm in length (Ringqvist et al, 1985). The hemodynamic specialist and both physicians in charge of the case agreed on an estimated “normal” caliber when such segment does not exist (Bermúdez et al, 2003). Obstructive CAD was defined as any luminal stenosis ≥ 50% (Kong and Rosati, 1980). Analyses were done using *Philips AlluraXper FD 20*® medical system software.

**Carotid intima media thickness (IMT) measurement**

Within 10 days of coronary angiography, all recruited subjects underwent carotid Doppler to determine carotid IMT. Ultrasound was performed with a *GE Vivid 7®* system equipped with a 13 MHz linear array imaging probe. The transducer was manipulated so that the near and far walls of the CCA became parallel to the transducer footprint and the lumen diameter was maximized in the longitudinal plane. An area 1 cm proximal to the carotid bifurcation was identified. The IMT measurement was obtained from four adjacent sites at 1mm intervals, and the average of the four measurements was used for analyses (Figure 1). All measurements were performed by investigators blinded to clinical and angiographic data. Upper normal average IMT is estimated to be up to 0.8 mm (Çelik et al, 2007).

**Hs-CRP level measurement**

Blood samples were withdrawn from all recruited subjects after completion of coronary angiography and sera were obtained by centrifugation of the blood for 10 minutes and then stored in several aliquots at - 70 °C until assayed. Highly sensitive CRP was measured using STAT-FAX reader using Accu-bind microplate ELISA kits provided by *Monbind Inc. lake fores, CA92630 USA*. The test was done by investigators blinded to clinical and angiographic data. The normal range of hsCRP level is considered 3 mg/l or less (Saglam et al, 2008).

**STATISTICAL ANALYSIS**

Data management and statistical analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21. Numerical data were summarized using means and standard deviations or medians and ranges. Categorical
Figure 1. Case no. 3, group 1: Male, 67 years old, hypertensive and smoker, with history of dyslipidemia. He is not diabetic and gives no family history of premature CAD. His coronary angiography revealed mixed CAE (type III) with obstructive CAD (Panel A and B). His average carotid IMT is 1.2 mm (Panel C).


Figure 2. Schematic representation of the study groups.
CAE: coronary artery ectasia, CAD: coronary artery disease.

RESULTS

Study population

During the study period, there were 61 patients with CAE out of 1611 coronary angiograms performed (3.78%). Of those, 35 patients (57%) showed mixed CAE with obstructive CAD “group 1” and 26 patients (43%) showed pure CAE with no obstructive CAD “group 2” (Figure 2). Of all patients found to have CAE, the mean age was 56±14 years. Eighty four percent were males, 67% were hypertensive, 16% had history of DM, 72% were smokers, 46% had dyslipidemia, 48% were obese and...
Table 1. Clinical characteristics of the studied groups*

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>P value</th>
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</thead>
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<tr>
<td>Age (yrs.)</td>
<td>Mean ±SD</td>
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<tr>
<td></td>
<td>55.4±13.1</td>
<td>55.9±14.4</td>
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<td>59.9±15.4</td>
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<td></td>
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<tr>
<td></td>
<td>30  85.7a</td>
<td>21  80.8b</td>
<td>14  53.8b</td>
<td>14  40.0a</td>
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<td>HTN</td>
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<td>17  65.4b</td>
<td>7  26.9b</td>
<td>10  28.6a</td>
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<td>5  19.2b</td>
<td>17  65.4b</td>
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<tr>
<td>Smoking</td>
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<td>19  73.1b</td>
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<td>12  34.3a</td>
<td>&lt;0.001</td>
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<td>Dyslipidemia</td>
<td>17  48.6</td>
<td>11  42.3</td>
<td>13  50.0</td>
<td>17  48.6</td>
<td>0.945</td>
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<td>Obesity</td>
<td>16  45.7</td>
<td>13  50.0</td>
<td>14  53.8</td>
<td>16  45.7</td>
<td>0.911</td>
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<td>Family history of</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>premature CAD</td>
<td></td>
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<td>Nitrate therapy</td>
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<td>30 (7-150)</td>
<td>45 (3-150)</td>
<td>30 (3-90)</td>
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<td>duration (Days)</td>
<td>(range)</td>
<td>(7-150)</td>
<td>(3-150)</td>
<td>(3-90)</td>
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</tbody>
</table>

*Similar letter superscripts in table indicate statistically significant difference.
DM: diabetes mellitus, HTN: hypertension, p < 0.05 is significant.

Table 2. Significant predictors of CAE*

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI for OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
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<tr>
<td>HTN</td>
<td>20.3</td>
<td>2.7</td>
<td>154.6</td>
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<tr>
<td>Absence of DM</td>
<td>23.3</td>
<td>3.0</td>
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<tr>
<td>Smoking</td>
<td>8.0</td>
<td>1.3</td>
<td>48.8</td>
</tr>
<tr>
<td>hs-CRP &gt; 3mg/L</td>
<td>4.4</td>
<td>2.2</td>
<td>8.6</td>
</tr>
</tbody>
</table>

*Adjusted for age and gender
OR: odds ratio, CI: confidence interval. DM; diabetes mellitus, HTN: hypertension, hs-CRP: high sensitivity C-reactive protein

49% had family history of premature CAD. The median duration of nitrate therapy in those patients was 45 (range: 3-150) days. Clinical characteristics of studied patients are illustrated in (Table 1).

Predictors of CAE

An age and gender-adjusted logistic regression model has been done using CAE as dependent factor, while age, gender, risk factor data (DM, HTN, smoking, obesity, dyslipidemia and family history of premature CAD), carotid IMT > 8 mm and hs-CRP value > 3 mg/L were used as independent factors. It was found that significant independent predictors for development of CAE are: hypertension, absence of DM, smoking and hs-CRP level > 3mg/L (Table 2).

Angiographic data

Among patients proved to have CAE, we found that the most common type according to Markis classification is type III (48%) followed by type IV (36%) and then type I (16%). Of note, no patients were found to have type II CAE in our study. The most commonly affected vessel was RCA (59%) followed by LAD (36%) then LCX (20%) and finally left
main coronary artery “LMCA” (3%). Notably, no patients were found to have three-vessel affection in type I CAE and no patients were found to have LMCA affection in type III CAE.

Clinical presentation

The commonest clinical presentation among all patients with CAE was stable angina (49%) followed by STEMI (36%) and then Non-ST segment elevation acute coronary syndromes “NSTE-ACS” (15%). Between groups analysis showed a statistically significant difference in the occurrence of STEMI between groups 1 and 4 (34% versus 11% respectively, P = 0.002), between groups 2 and 3 (39% versus 4% respectively, P = 0.002) and between groups 2 and 4 (39% versus 11% respectively, P = 0.002). Of the 22 patients with CAE who presented with STEMI, the predominant type of CAE was type IV (17 patients), moreover, there was a good correlation between MI territory and the ectatic vessel in 21 patients.

Carotid IMT

The mean carotid IMT among all patients with CAE was 1±0.2 mm. Between groups analysis showed a statistically significant difference in the mean carotid IMT between groups 1 and 4 (1±0.2 mm versus 1.4±0.4 mm respectively, P < 0.001) and between groups 2 and 3 (1±0.1 mm versus 0.4±0.2 mm respectively, P < 0.001) (Figure 3).

Hs-CRP levels

The mean hs-CRP level among all patients with CAE was 6±2 mg/L. Between groups analysis showed a statistically significant difference in the mean hs-CRP level between groups 1 and 2 (7±2 mg/L versus 6±2 mg/L respectively, P < 0.001), between groups 1 and 4 (7±2 mg/L versus 3±0.8 mg/L respectively, P < 0.001) and between groups 2 and 3 (6±2 mg/L versus 1±0.6 mg/L respectively, P < 0.001) (Figure 4).

DISCUSSION

Coronary artery ectasia (CAE) remains an understudied and underreported variant of CAD in the literature. Our study is a prospective observational case-control one that aimed mainly to describe clinical and angiographic characteristics of CAE together with approaching the mysterious domain of ectasia’s pathogenesis through studying its association with carotid IMT and hs-CRP levels.

Regarding clinical characteristics of patients with CAE, our study showed male gender predominance (84% of CAE). This observation goes, to a large extent, with those of other large observational studies; Nyamu et al., 2003; Nisar et al., 2013 and Amirzadegan et al., 2014 also showed a striking male distribution of the phenomenon. Importantly, an age- and gender-adjusted logistic regression analysis in the present study showed that the significant independent predictors for CAE are: hypertension, absence of DM, smoking and hs-CRP value > 3 mg/L. Bermúdez et al., 2003 did a similar logistic regression model that revealed, like our results, that the presence of DM is significantly related to absence of CAE (OR = 0.65; 95% CI, 0.43-0.98, P = 0.03). They also found that male gender is significantly associated with presence of CAE (OR = 3.33; 95% CI, 1.81-6.13, P < 0.01), a result not found in the current study. Notably, they didn’t have any work on markers of
Coronary artery ectasia and markers of atherosclerosis

Figure 4. Box plot of hs-CRP level (mg/L) in different study groups.

HS-CRP: high sensitivity C-reactive protein.

Atherosclerosis including carotid IMT or hs-CRP. This gives novelty to the current study. The fact that patients with CAE show minimal prevalence of DM, and that the presence of DM is negatively associated with CAE is noteworthy and actually, could not be easily explained. However, one explanation might lie in the association of diabetes with a reduction in endothelium-dependent vasodilation, caused by alterations in the synthesis and inhibition of nitric oxide, which seems to play a significant role in the development of CAE. Diabetes mellitus primarily affects the intimal, but not the medial layer of the vessel, thus inducing a state of insidious and evolving "negative remodeling" (Schoenhagen et al., 2001).

Our findings revealed that the most common type of CAE (per Markis classification) was type-III (48%) and that the most commonly affected vessel by the phenomenon was RCA (59%). These results are concordant with the wealth of data in the literature except for few studies that showed type-IV CAE to be the most common (Ahmed et al., 2013; Sultana et al., 2011) and others showing type-I is the predominant type and LAD is the most frequently affected vessel (Nyamu et al., 2003). Interestingly, the above mentioned contradictory data regarding angiographic distribution of CAE came exclusively from Asian population, pointing to possible racial and/or genetic differences in the vascular distribution of CAE.

A considerable proportion of patients with CAE (36%) presented with STEMI in the current study; this comes to be statistically significant when comparing this figure to normal subjects ‘group 3’ (only 4%) and to those with obstructive CAD without ectasia ‘group 4’ (11%) (P = 0.002). A similar result was provided by Amirzadegan et al., 2014. On the opposite hand, some data (Bermúdez et al., 2003) revealed no significant difference in the incidence of MI when comparing patients with CAE to those without. Overall, the observations of association of CAE with MI, albeit not significant in some series, are convincing that this phenomenon is not a benign one.

To the best of our knowledge, there are very limited data in the literature studying pathogenic mechanisms of the usual form of CAE. These efforts are divided into two main domains: the atherosclerotic theory (as surrogated by carotid IMT) and/or the inflammatory theory (as surrogated mainly by hs-CRP levels and other markers). All groups studying hs-CRP levels in patients with CAE provided a consistent result that hs-CRP is significantly higher in patients with CAE compared to patients with obstructive CAD and patients with normal coronaries (Ozbay et al., 2006; Turhan et al., 2004; Ammar et al., 2013). Our results were identically similar to those in the literature in that levels of hs-CRP were significantly higher in those with mixed CAE ‘group 1’ than patients with obstructive CAD without ectasia ‘group 4’ and in patients with pure CAE ‘group 2’ when compared to those with normal coronaries ‘group 3’. These data collectively reflects a more intense inflammatory process in those patients.

Despite the above mentioned work on levels of inflammatory markers, atherosclerosis remains the most widely accepted pathogenic theory underlying CAE. Definite state-of-the-art proof of the atherosclerotic hypothesis could come only from studies using coronary artery in-vivo biopsies. However, such studies do not exist due to understandable reasons related to major
risks imposed. Therefore, many surrogate measures of in-vivo atherosclerotic burden have been used in the literature, and carotid IMT is one of the most widely accepted. Carotid IMT has been shown to be significantly higher in CAE patients versus normal in one study (Çelik et al., 2007) supporting the above mentioned atherosclerotic theory. However, a true threat to atherosclerosis as a stand-alone explanation for CAE comes from the puzzling results provided by Yetkin et al., 2005 who revealed that carotid IMT was significantly lower in those with mixed CAE than that measured in a similar number of patients with obstructive CAD without ectasia. Interestingly, the present study results came concordant with the supporting component in the literature for the atherosclerotic theory on one hand and with the puzzling component on the other. We revealed a significantly higher carotid IMT in patients with pure CAE ‘group 2’ that those with normal coronaries ‘group 3’ similar to Çelik et al., 2007. We also showed carotid IMT to be significantly lower in those with mixed CAE with obstructive CAD ‘group 1’ when compared to patients with obstructive CAD without ectasia ‘group 4’; this was similar to the puzzling results of Yetkin et al., 2005. Significantly lower carotid IMT in patients with mixed CAE and CAD than those with obstructive CAD alone (as shown in our study) is suggesting that CAE may not share the same pathological mechanism with atherosclerosis. Explanation for such a discrepancy could be as follows: first, we showed that absence of DM is a significant predictor for CAE and it is well known that DM is classically associated with increased carotid IMT (Kawamori et al., 1992). Second, hs-CRP (as a surrogate marker for inflammatory response) has been shown in the present study to be significantly higher in patients with mixed CAE and CAD than those with CAD alone.

CONCLUSION

At our institution, the significant independent clinical predictors for development of CAE are: hypertension, smoking, absence of DM and level of hs-CRP > 3 mg/L. Atherosclerosis is an important underlying pathogenic mechanism for CAE but may not be the only plausible one. Other additional factors may be involved such as inflammatory response.

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None

CONFLICTS OF INTEREST

None

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