Isolated coronary artery ectasia debate: Inflammation versus atherosclerosis

Eid Mohamed Daoud, Ayman Ahmed Abdelaziz *, Nahed Abdallah Hassan

Cardiology Department, Mansoura Faculty of Medicine, Egypt

Received 21 March 2012; accepted 9 June 2012
Available online 12 July 2012

Abstract Background: The underlying pathogenesis of isolated coronary artery ectasia (CAE) is still unknown. The aim of this study was to shed light on the potential mechanisms underlying the development of isolated CAE and its relation to carotid intima media thickness (IMT) and certain inflammatory markers especially adhesion molecules and uric acid.

Methods: The study included 16 patients with isolated CAE, 16 patients with obstructive coronary artery disease (CAD) without CAE, and 10 gender and age matched subjects with normal coronary arteries as control group. All patients underwent diagnostic coronary angiography, B-mode ultrasonography to measure carotid IMT, and serum levels of soluble intercellular adhesion molecule (ICAM-1), E-selectin and uric acid.

Results: Serum ICAM-1 levels were found to be significantly higher in patients with isolated CAE compared to CAD and control subjects \((p=0.0001)\). E-selectin levels showed no difference between the three groups, while serum uric acid was significantly higher in patients with isolated CAE and patients with obstructive CAD compared to control group \((p=0.004)\). There were no difference in carotid IMT between isolated CAE and CAD. Univariate analysis showed that the carotid IMT, serum levels of ICAM-1, E-selectin, and uric acid were related with CAE. ICAM-1 was the independent variable most strongly associated with CAE by multiple linear regression analysis \((p = 0.0001)\).

Conclusion: Isolated CAE reflects atherosclerosis associated with high grade vascular inflammation out of proportion to, atherosclerotic involvement. Serum levels of ICAM-1 were the most independent predictor of vascular inflammation.

© 2012 Egyptian Society of Cardiology. Production and hosting by Elsevier B.V. All rights reserved.

1. Introduction

Coronary artery ectasia (CAE) has been defined as localized or diffuse non obstructive lesions of one of the epicardial coronary arteries with a luminal dilatation exceeding the 1.5-fold of normal adjacent segment or vessel diameter.\(^5\)
Isolated CAE, in which coronary artery stenosis, valvular heart disease, and other cardiac disorders are not present. Isolated CAE comprises a small portion of total CAE cases, with an incidence of 0.1–0.79%

Previous studies have shown that CAE is an angiographic finding whose prevalence in different reports is in the range of 0.3–5.3% in angiographic examination and is observed in 1–5% of patients with angiographic evidence of CAD. It is estimated that 50% of CAE is related to atherosclerosis, whereas 20–30% of cases may be due to congenital anomalies. Histological changes in CAE were identical to those found in atherosclerotic lesions (diffuse hyalination, intimal and medial damages). There is now general agreement that atherosclerosis is an inflammatory disease appeared in different clinical entities, including atheromatous development, plaque rupture, coronary spasm, delayed coronary flow, coronary microvessel dysfunction, silent myocardial ischemia, and restenotic process.

Carotid IMT is widely used as a surrogate marker for atherosclerotic disease. Carotid IMT measured by ultrasound has been shown to be correlated with CAD as defined by angiography.

Li hypothesized that CAE might be associated with inflammation; however the association between inflammation and CAE from published data has been controversial. Serum uric acid level was reported to be associated with the presence of CAD and coronary artery ectasia, coronary blood flow, and coronary collateral flow. Moreover, serum uric acid level was also shown to be associated with markers of early atherosclerosis like carotid intima-media thickness and endothelial dysfunction like brachial artery flow mediated dilatation.

2. Aim of the work

The aim of our study was to shed light on the potential mechanisms underlying the development of isolated coronary artery ectasia and its relation to carotid IMT and certain inflammatory markers especially adhesion molecules and uric acid.

3. Patients and methods

3.1. Study population

The study population was prospectively selected from consecutive patients who underwent coronary angiography in our catheterization laboratory, Mansoura Medical Specialized hospital, Mansoura University, Egypt between July 2011 and January 2012.

Coronary angiography was done for these patients due to the presence of typical angina pain and/or positive results of non-invasive tests suggesting the presence of myocardial ischemia.

Written consents were taken from all the patients.

They were divided into three groups:

Group I: 16 patients with CAE without obstructive CAD pressure (CAE group) (mean age 53.31 ± 5.40 years).
Group II: 16 patients with obstructive CAD without CAE (CAD group) (mean age 54.87 ± 5.72 years).
Group III: 10 age and sex matched subjects with normal coronary arteries (control group) (mean age 52.40 ± 6.41 years).

3.2. Exclusion criteria

- Patients with CAE and severely concomitant CAD.
- Patients with acute coronary syndromes, and acute myocardial infarction.
- Heart failure.
- Valvular heart disease.
- Conduction disturbance.
- Gastrointestinal motility disorders.
- Thyroid disorders.
- Liver and renal impairment.
- Autoimmune disease.
- Uncontrolled hypertension.

3.3. Coronary angiography

Coronary angiography was performed by the Judkins technique for all studied patients. Coronary artery ectasia was defined as luminal dilatation of 1.5-fold or more of the adjacent normal coronary segment. Patients with CAE without obstructive CAD defined as localized or diffuse dilatation of coronary arteries without significant stenosis. Obstructive CAD was defined as the stenosis of epicardial coronary artery ≥ 70% by coronary angiography.

3.4. Laboratory measurements

Serum levels of circulating ICAM-1 and E-selectin were determined by a commercially available sandwich ELISA technique (Ray Biotech. Inc. for E selectin and R and D system. Inc. Minneapolis for ICAM-1).

The procedure was performed according to the manufacturer’s instructions. Briefly, a conjugated monoclonal antibody against ICAM-1 and E-selectin was added to microtitre plates coated with a murine monoclonal IgG antibody recognizing a different epitope of the corresponding molecule after incubation with samples or standards inappropriate dilution, the color reaction was developed with tetramethylbenzidine (TMB) and the plates were read on an automated multiscaner at 450 nm. All measurements were performed in duplicate.

Serum level of uric acid was performed by standard automated analyzer (Cobas Integra 400 plus S.N. 500237).

3.5. Carotid intima media thickness measurement

B-mode ultrasound examinations were performed with (vivid 3 pro, General Electric, Vingmed Ultrasound, Horten, Norway) equipped with a 7.5 MHz linear array transducer. The right common carotid artery (CCA) was examined. A region of 1 cm proximal to carotid artery bifurcation was identified. Carotid IMT was evaluated as the distance between the lumen–intima interface and media adventitia interface, avoiding...
plaque sites. The IMT was measured on the frozen frame of a suitable longitudinal image. The IMT was measured from four contiguous sites at 1-mm intervals and the average of the four measurements was used.  

3.6. Statistical analysis

All data were analyzed using a SPSS software package (version 17.0, SPSS Inc, Chicago, Illinois, USA). Continuous variables were expressed as mean ± SD, and categorical variables were expressed as percentage. Comparison of categorical and continuous variables was performed using Chi-square test and independent t-test, respectively. The correlation between CAE and clinical, IMT, and laboratory data was determined with Spearman and Pearson correlation analysis. Multivariate logistic regression analysis was performed to define the independent variables associated with CAE. A p value of < 0.05 was considered statistically significant.

4. Results

Baseline demographic and clinical characteristics data are summarized in Table 1. There was no difference as regards age, sex, and different risk factors including diabetes mellitus, hypertension, smoking, family history of CAD and Dyslipidemia among the three groups.

Patients with isolated CAE showed significant increase in serum levels of ICAM-1 compared with obstructive CAD as well as angiographically normal control group (672.8 ± 91.05 pg/dl, 430.6 ± 90.31 pg/dl, and 298.0 ± 57.69 pg/dl, respectively; p < 0.0001, Table 2, Fig. 1). On the other hand E-selectin levels showed no difference between the three groups, while serum uric acid was found to be higher in patients with isolated CAE and patients with obstructive CAD compared to control group (6.77 ± 1.3 mg/dl, 6.61 ± 1.1 mg/dl, and 5.1 ± 1.2 mg/dl, respectively; p < 0.004, Table 2). There was no difference in serum uric acid between patients with isolated CAE and obstructive CAD.

There was no difference in carotid IMT between isolated CAE and obstructive CAD (Table 2); but when compared to control group, carotid IMT was significantly higher in both groups than control subjects with angiographically normal coronary arteries (0.90 ± 0.79 mm, 0.89 ± 0.05 mm, and 0.68 ± 0.08 mm, respectively; p < 0.0001, Table 2, Fig. 2).

In this study, four variables were associated with isolated CAE including carotid IMT, ICAM-1, E-selectin, and uric acid levels in univariate analysis (Table 3). However we found no significant correlation between isolated CAE and age, sex, hypertension, diabetes mellitus, smoking, dyslipidemia, and family history of CAD.

### Table 1 Baseline clinical characteristics (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>CAE (n = 16)</th>
<th>CAD (n = 16)</th>
<th>Control (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.31 ± 5.40</td>
<td>54.87 ± 5.72</td>
<td>52.40 ± 6.41</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>13 (81.3%)</td>
<td>12 (75%)</td>
<td>8 (80%)</td>
<td>NS</td>
</tr>
<tr>
<td>HTN, n (%)</td>
<td>5 (31.31%)</td>
<td>4 (25%)</td>
<td>2 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>4 (25%)</td>
<td>4 (25%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>9 (56.3)</td>
<td>8 (50%)</td>
<td>5 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>5 (31.3%)</td>
<td>3 (18.8%)</td>
<td>2 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Family history, n (%)</td>
<td>4 (25%)</td>
<td>4 (25%)</td>
<td>1 (10%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

HTN: hypertension, DM: diabetes mellitus, NS: no significant difference.

### Table 2 Comparative analysis of carotid IMT, and plasma level of inflammatory markers among different study groups.

<table>
<thead>
<tr>
<th></th>
<th>CAE (n = 16)</th>
<th>CAD (n = 16)</th>
<th>Control (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT (mm)</td>
<td>0.90 ± 0.79</td>
<td>0.89 ± 0.058</td>
<td>0.68 ± 0.081</td>
<td>0.0001** ****</td>
</tr>
<tr>
<td>ICAM-1 (ng/dl)</td>
<td>672.8 ± 91.05</td>
<td>430.6 ± 90.31</td>
<td>298.0 ± 57.69</td>
<td>0.0001** ****</td>
</tr>
<tr>
<td>E-selectin (ng/dl)</td>
<td>68.31 ± 21.25</td>
<td>62.25 ± 11.92</td>
<td>55.70 ± 12.05</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>6.77 ± 1.30</td>
<td>6.61 ± 1.13</td>
<td>5.13 ± 1.23</td>
<td>0.004***</td>
</tr>
</tbody>
</table>

* Ectasia versus CAD.
** Ectasia versus control.
*** CAD versus control, IMT: intima media thickness.
Multiple linear regression analysis showed that only ICAM-1 was the independent variable most strongly associated with isolated CAE (Table 4).

5. Discussion

Isolated CAE was defined as CAE without significant stenosis or occlusion of the coronary artery. Isolated coronary ectasia may also be present with stable angina, positive treadmill test, increased levels of biochemical markers or even myocardial infarction, by means of reduced and sluggish flow, thrombus formation, and vasospasm.

Coronary artery ectasia resembles atherosclerosis in several respects. One piece of supporting evidence for this statement is that the two diseases (CAE and CAD) have similar risk factors. Secondly; patients with CAE commonly have co-morbid CAD. Third, the two conditions exhibit similar histopathological features.

Coronary artery ectasia is considered to be an original form of vascular remodeling in response to atherosclerosis. However, it is not clear why some patients develop CAE while most do not.

Although atherosclerosis is supposed to be responsible for more than 50% of CAE, the underlying pathogenesis of CAE is still unknown, and a definite link between atherosclerosis and ectasia has not been confirmed. Furthermore, coronary aneurysms are seen in association with systemic inflammatory vasculitis (e.g., polyarteritis nodosa, Kawasaki disease, Takayasu arteritis, Behcet’s disease), connective tissue disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, scleroderma, ankylosing spondylitis), hereditary collagen defects (e.g., Ehlers-Danlos syndrome, Marfan syndrome, hereditary hemorrhagic telangiectasia), bacterial infections and congenital malformations. The failure of conventional risk factors for atherosclerosis to discriminate between isolated CAE and the mixed forms urges more search for specific risk factors, genetic or metabolic for explaining the morphological difference.

The aim of our study was to shed light on the pathogenesis of isolated CAE and its relation to carotid intima media thickness as a measure of atherosclerosis and certain inflammatory markers especially adhesion molecules and uric acid.

In our study, we did not find significant difference in baseline clinical characteristics between isolated CAE and CAD group. This is in contradiction to previous data showed that most patients with isolated CAE were men (91.2%), smokers (56.5%), and younger than patients without ectasia, and that only diabetes was independently associated with the absence of ectasia. This difference may be attributed to our small sample size.

The higher concentration of soluble ICAM-1 in patients with isolated CAE in comparison with CAD and control group suggesting the presence of a more severe and extensive chronic inflammation in the coronary circulation in these patients. Yilmaz et al. found that patients with isolated CAE have raised levels of ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) and E-selectin. More ever, Turhan et al. found elevated levels of ICAM-1 and VCAM-1 in patients with CAE and obstructive CAD plus CAE compared with subjects with normal coronary artery and obstructive CAD.

Tokgozoglu et al. studied 43 patients with CAE, and found that serum IL-6 levels were significantly higher in patients with
CAE compared to normal controls. Turhan et al. reported that the levels of CRP, were significantly higher in patients with isolated CAE. Maged et al. found that IL-6 and hs CRP as inflammatory markers were elevated in patients with CAE and also were elevated in patients with coronary artery stenosis.

Multiple linear regression analysis showed that only ICAM-1 was the independent variable most strongly associated with isolated CAE (Table 4). This means that coronary ectasia develops in an intensely inflamed vascular wall, which predisposes to plaque instability and increased risk of adverse cardiovascular events despite preservation of the coronary lumen. Accordingly, CAE has been suggested to be a destructive inflammatory lesion of the vascular wall.

Adhesion molecules, integrins and cytokines are mechanically interrelated. Vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin are adhesion molecules that are expressed on the endothelial cell membrane and mediate the adhesion and transmigration of leukocytes to vascular endothelium. Soluble shedded forms of these molecules are found in plasma and their concentration is regarded as a surrogate marker of cellular expression. E-selectin mediates the initial, low-affinity leukocyte-endothelial cell interaction that is manifested as leukocyte rolling. This transient binding results in further leukocyte activation and subsequent firm adhesion and trans endothelial migration of leukocytes, both of which are mediated by interactions between members of the integrin and immunoglobulin superfamily of cellular adhesion molecules: ICAM-1 and VCAM-1. Accordingly, ICAM-1 is an indicator of the cellular activation that accompanies inflammation.

In our study, we observed a significant increase in serum uric acid levels in patients with isolated CAE and patients with obstructive CAD, compared to subjects with angiographically normal coronary arteries. Uric acid as a marker of increased xanthine oxidase activity which converts xanthine or hypoxanthine to uric acid, is an important mediator of inflammatory responses and cellular damage. The ability of xanthine oxidase to generate superoxide free radicals is important in stimulating the expression of adhesion molecules by leukocytes and in the activation and adherence of leukocytes to damaged endothelium a pre-requisite for endothelial injury. Furthermore, via release of reactive oxygen species, activation of xanthine oxidase activates matrix metalloproteinases (MMP-3) species which may play a role in the pathogenesis of isolated CAE development through increased proteolysis of extracellular matrix proteins. Matrix degrading enzymes may cause severe disruption of the internal elastic lamina providing a gateway for the inflammatory cells to extend from the intima into the media, elaborate matrix proteases, degrade the collagen and elastin fibers, weaken the arterial wall integrity, and ultimately promote an ectatic transformation of the wall.

Nihat et al. observed a significant increase in serum uric acid levels in patients with CAE or CAD, compared to the controls.

Patients with isolated CAE had higher carotid IMT compared to control subjects with angiographically normal coronary arteries (0.90 ± 0.79 versus 0.68 ± 0.08 mm, \( p < 0.0001 \)). In addition, we detected a significant positive correlation between the presence of CAE and carotid IMT (\( r = 0.591, p < 0.0001 \)). This indicates the presence of an association between increased carotid IMT and isolated CAE, suggesting that atherosclerosis may be involved in the pathogenesis of isolated CAE in the adult population. Our results were in contrary to that of Jang et al. who showed that carotid IMT was significantly less in patients who had isolated CAE and cardiac syndrome X compared with the CAD suggesting that there was no atherosclerotic involvement in patients with isolated CAE and isolated CAE is resulting from a different pathogenesis.

Study limitation: The first limitation of this study was that the angiographic definition of normal coronary arteries relies on axial contrast angiograms of the vessel lumen which underestimate the presence of atherosclerotic plaque. The second limitation was the small sample size.

6. Conclusion

Isolated CAE reflects atherosclerosis associated with high grade vascular inflammation out of proportion to atherosclerotic involvement. Serum level of ICAM-1 was the most independent predictor of vascular inflammation associated with isolated CAE.

Further experimental investigations are needed to reveal the molecular mechanisms involved in ectasia, and more intensive investigation and understanding of the pro- and anti-inflammatory circuits that operate in isolated CAE may be warranted.

References


