Introduction

Coronary artery ectasia has been a well recognized angiographic finding for decades, characterized by abnormal dilatation of the coronary arteries. Patients with coronary artery ectasia typically present with angina, and are at risk for myocardial infarctions and sudden cardiac death due to slow flow, dissection, coronary vasospasm, and/or intracoronary thrombosis.

The origin of coronary artery ectasia is considered to be congenital in about 10 – 20 % of the cases ***(Swanton et al., 1978),*** whereas acquired coronary artery disease accounts for the majority of the cases and is most commonly attributed to atherosclerosis, with less frequent etiologies being inflammatory and connective tissue diseases such as scleroderma, Ehler-Danlos, systemic lupus erythematosus, Kawasaki disease, bacterial infections and cardiac lymphomas ***(Kruger et al., 1999 and Matayoshi et al., 1999)***.

Coronary artery ectasia is often viewed as a variant of obstructive coronary atherosclerosis ***(Schoenhagen at al., 2001 and Li Jian-jun et al., 2011),*** and is increasingly thought to be an inflammatory-relating disease ***(Kocaman et al., 2008).*** Where inflammation results in exaggerated positive vascular remodeling, which is described as an expansion of the external elastic membrane that allows considerable plaque accumulation, without luminal loss ***(Li et al., 2009).***

In a recent study, Red Cell Distribution Width was significantly related with major adverse cardiac events (MACE) in patients with heart failure even after the adjustment of hematocrit values ***(Felker et al., 2007).*** In another study, researchers have shown that increased Red Cell Distribution Width is independently related to long-term mortality in patients with coronary artery disease without anemia ***(Tonelli et al., 2008 and Uyarel et al., 2011).*** But, in these studies, underlying mechanisms related to increased MACE remained unclear ***(Mustafa et al., 2012).*** In a previous study that included a coronary ectasia group versus a normal angiography group, the Red Cell Distribution Width was found to be higher in the coronary ectasia group ***(Dodgu et al., 2012).***

Although many studies have shown that serum uric acid (SUA) levels are an important independent factor in development of cardiovascular diseases (CVD), no informative data regarding the pathogenesis of the disease is available in any of these studies ***(Freedman et al., 1995; Fessel et al., 1980 and Culleton et al., 1999)*** Serum uric acid level was reported to be associated with atherosclerotic markers such as several inflammation markers**,** ***(Ruggiero et al., 2006)*** oxidative stress and endothelial dysfunctions ***(Kato et al., 2005 and Erdogan et al., 2005)*** A study also showed that higher levels of serum uric acid was associated with atherogenesis independent of hypertension ***(Tavil et al., 2008).*** Regardless of the underlying

mechanism, high levels of serum uric acid increase the risk of atherosclerosis. A previous study demonstrated a significant increase in serum uric acid levels in patients with coronary artery ectasia or coronary artery disease, compared to the controls. However, no significant relationship between serum uric acid level and the extent of coronary artery ectasia involvement was found ***(Nihat et al., 2009).***

Aim of the Work

To evaluate the relationship between the inflammatory process and the development of coronary artery ectasia, using the red blood cell distribution width and serum uric acid levels as inflammatory biomarkers.

Chapter 1:

Coronary Artery Ectasia

Coronary artery ectasia (CAE) is a well recognized, relatively common abnormality of the coronary anatomy that has gained a lot of attention over the past few decades as a separate entity of coronary artery disease (CAD) ***(Akyurek et al., 2003).*** Its importance comes from the fact that patients suffering from CAE may present with acute coronary syndrome (ACS) just like those having stenotic atherosclerotic CAD.

The condition was first described by **Bourgon** in 1812 as a postmortem finding, while the term "ectasia" was first coined by **Bjork** in 1966**.**

The advent of cardiac catheterization allowed the diagnosis to be made in life and helped more with determination of associations with the disease ***(Hartnell et al., 1985)***. Yet, its etiology, pathophysiology, treatment and prognosis are all still questionable and need further research and studies.

Definition:

CAE is angiographically defined as an abnormal irregular dilatation of an arterial segment at least 1.5 times more than an adjacent healthy reference segment or an adjacent normal vessel ***(Hartnell et al., 1985).***

CAE may occur alone in a condition known as "dilated coronopathy" or in association with atherosclerotic CAD.

Incidence:

CAE can be found in 0.22% to 1.4% of autopsy series ***(Hartnell et al., 1985)***. In the largest series from the CASS registry, CAE was found in 4.9% of more than 20000 coronary angiograms they reviewed ***(Swaye et al., 1983).***

Table (1): Prevalence of coronary ectasia in angiographic series

Source	Number of subjects	Prevalence (%)
Swaye et al.	20.087	4.9
Giannoglou et al.	10.524	2.7
Tunick et al.	8.422	0.2
Hartnell et al.	4.993	1.4
Markis et al.	2.457	1.2

All three coronary vessels can be affected by CAE, but in almost 75% of patients an isolated artery is ectatic ***(Al Harthi et al., 1991).***

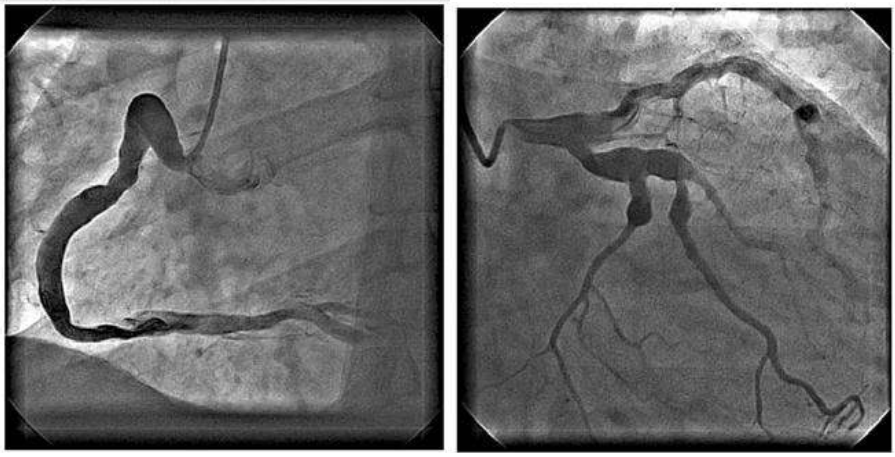
The proximal and mid segments of the RCA are the most commonly involved in CAE, followed by the LAD and LCX, LMCA is the least affected vessel, however, with regard to CAD, the LAD is most commonly affected, followed by the RCA and LCX ***(Giannoglou et al., 2006).*** The reason for the higher RCA predisposition to CAE is not well understood. In patients with CAD coexisting with CAE, 34% of the stenotic

lesions were in the vessels affected by the ectatic process, while 65% were in the non-ectatic vessels. It has also been demonstrated that total CAD severity, expressed as the number of coronary stenotic lesions per patient, is found to be equivalent in patients with CAD with and without coexisting CAE ***(Demopoulos et al., 1997).***

Classification of CAE:

The first attempt for classification was proposed by ***Markis et al. in (1976)***, who classified CAE, based on the extent of ectatic involvement in descending order of severity into four 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.
- Type IV, localized or segmental ectasia.



(A) (B)

Fig. (1): Different angiographic views showing: (A) Diffuse RCA ectasia (B) Diffuse ectasia of LMCA, proximal LAD&LCX focal ectasia ***(Helmy et al., 2009)***

CAE has also been classified according to the anatomical shape of the ectatic segment, into fusiform or saccular types ***(Befeler et al., 1977).*** Older studies preferred the term 'coronary aneurysm' for the more discrete and saccular type ectatic segments, reserving the term 'ectasia' for the fusiform diffuse vessel involvement ***(Tunick et al., 1990).***

Etiology of CAE:

The origin of CAE is considered to be congenital in about 10% - 20% of the cases with the remainder being acquired ***(Swanton et al., 1978).***

Congenital CAE was found to be frequently associated with other cardiac abnormalities such as bicuspid aortic valve, aortic root dilatation, ventricular septal defect, pulmonary

stenosis as well as cyanotic heart diseases ***(Chugh et al., 2004 and Ucar et al., 2005).***

Acquired CAE accounts for the majority of the cases and is most commonly attributed to atherosclerosis ***(Kruger et al., 1999).***

Less frequent etiologies included inflammatory and connective tissue diseases such as scleroderma ***(Chaithiraphan at al., 1973),*** Ehler-Danlos syndrome ***(Imahori et al., 1969),*** systemic lupus erythematosus ***(Matayoshi et al., 1999),*** Kawasaki disease ***(Hiraishi et al., 1981),*** polyarteritis nodosa ***(Tang et al., 1971),*** bacterial infections ***(Davidson et al., 1991),*** and cardiac lymphomas ***(Gardiner at al., 1989).***

Localized iatrogenic ectasia has been reported after angioplasty in about 5% of cases and particularly after extensive dissection ***(Vassanelli et al., 1989 and ETB al et al., 1991).*** It has also been described following directional coronary atheroctomy ***(Krolick et al., 1992 and De Cesare et al., 1992),*** and pulsed laser angioplasty ***(Preisack et al., 1992).***

In a large study that included 792 lesions, ***Oikawa et al. (2008)*** showed that the prevalence of coronary artery aneurysm following directional coronary atherectomy was low (2.7%) with a favorable long-term clinical outcome.

Pathogenesis and mechanism of CAE:

Traditionally, the development of coronary artery disease (CAD) was described as a gradual growth of plaques within the intima of the vessel. The outer boundaries of the intima, the

media and the external elastic membrane (EEM), were thought to be fixed in size. In this model plaque growth would always lead to luminal narrowing and the number and severity of angiographic stenoses would reflect the extent of coronary disease. However, histologic studies demonstrated that certain plaques do not reduce luminal size, presumably because of expansion of the media and EEM during atheroma development ***(Schoenhagen et al., 2001).***

Using IVUS, ***Ge et al. (1993)*** reported that the EEM area of atherosclerotic segments was significantly larger than that of proximal segments. Further histologic and IVUS studies demonstrated that arterial remodeling could be bidirectional.

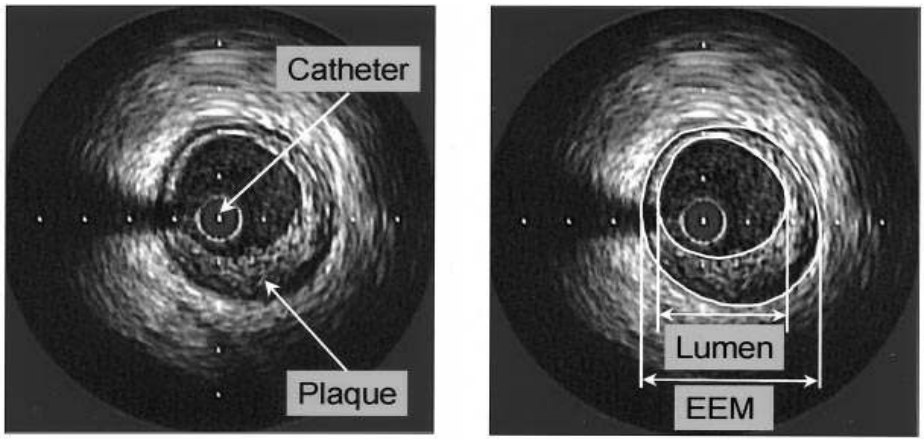


Fig. (2): Intravascular ultrasound images show tomographic sections of the vessel, including lumen, vessel wall and adventitia ***(Schoenhagen et al., 2001)***

Manginas et al. (2006) speculated that CAE occurs due to two different mechanisms in two distinct patient groups: 1. commonly in patients with concomitant CAD due to severe and

chronic arterial inflammation and 2. subjects without coronary atherosclerosis as a result of exogenous interstitial NO vascular over stimulation.

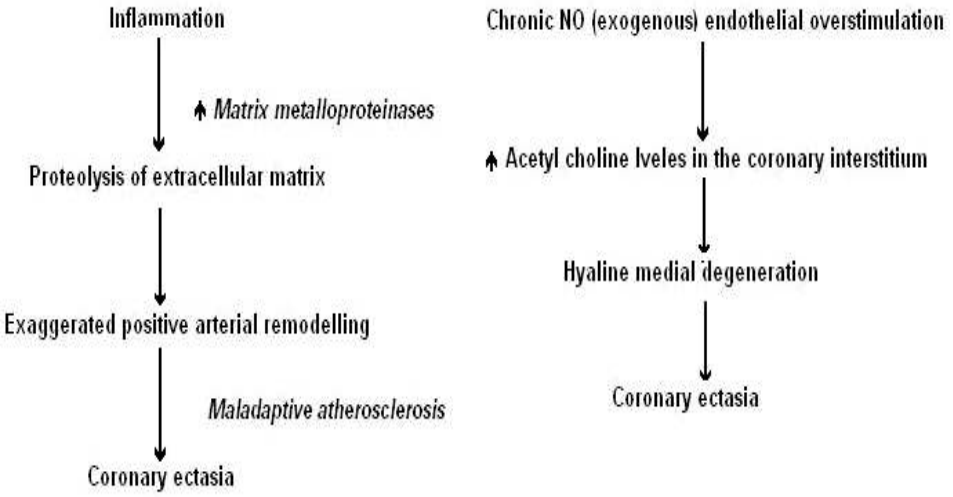


Fig. (3): Pathogenetic mechanisms of coronary ectasia ***(Aboeata et al., 2012)***

In the first group, the causative mechanisms of abnormal luminal dilation in CAE are unknown. CAE is often viewed as a maladaptive process of atherosclerosis ***(Kruger et al., 1999 and Schoenhagen et al., 2001)*** and can be regarded as a consequence of extensive positive remodeling ***(Yetkin et al., 2005).***

The major precursor of vascular remodeling is probably tissue inflammation. This hypothesis is supported by several studies linking the presence of CAE with elevated inflammatory markers such as plasma interleukin-6 ***(Tokgozoglu et al., 2004)***, plasma soluble adhesion molecules: V-CAM, I-CAM, and E-selectin ***(Turhan et al., 2005)***, and C-

reactive protein (CRP) ***(Adiloglu et al., 2005 and Saglam et al., 2007)***.

Sahin et al. (2008) showed that plasma neopterin, which is a marker of immune activation and macrophage activity, is significantly higher in patients with isolated CAE.

Kocaman et al. (2008) found that patients with isolated CAE had increased total and differential leukocytic counts, supporting the view that increased inflammation and leukocytosis can lead to the coronary ectatic process without visible atherosclerosis, and that leucocytes may play a critical role in this condition.

Hemodynamic conditions (flow, wall stretch, shear stress) may also act as signals or triggers for vascular remodeling ***(Gibbons et al., 1994; Dzau et al., 1993 and Langille et al., 1996)*** resulting in the synthesis or activation of mediators for cell growth, apoptosis, migration and changes in extracellular matrix ***(Cowan et al., 1996).*** The composition of extracellular matrix is regulated by matrix-metalloproteinase (MMP) activity, which selectively degrades the extracellular matrix components and may play an important role in the remodeling response ***(Nagase et al., 1999; Ye et al., 1998 and Dolerry et al., 1995).*** Patients with CAE were found to have a higher percentage of the 5A/5A polymorphism of the metalloproteinase-3 (MMP-3), compared to patients with obstructive coronary lesions ***(Lamblin et al., 2002).*** Over-

expression of MMP-3 may lead to enhanced proteolysis of various matrix proteins, such as proteoglycans, laminin, fibronectin and collagen types III, IV, V, and IX resulting in excessive vessel wall dilatation.

Another marker of inflammation, soluble lectin-like oxidized low density lipoprotein receptor-1, was found to be involved in multiple phases of vascular dysfunction, including endothelial dysfunction, initiation of plaque rupture and restenosis. ***Balin et al. (2012)*** found this marker to be significantly higher in CAE, compared to patients with normal coronaries, suggesting its involvement in pathogenesis of CAE.

The second group that **Manginas** mentioned involves chronic over stimulation of the endothelium with excessive nitric oxide (NO) and NO donors leading to abnormal coronary dilatation ***(Sorrell et al., 1998).***

NO is an endogenous vasodilator, however beyond its vasodilating actions, NO can resist inflammatory activation of endothelial functions such as the expression of vascular adhesion molecule-1 (VCAM-1) ***(Libby et al., 2006)***.

In normal vessels and under normal exposure, endothelial NO production is considered to be atheroprotective. However, on pathophysiological bases, chronic over stimulation of endothelium by NO might be a probable mechanism that predisposes to CAE ***(Sorell, 1996).***

Beckman et al. (1996) demonstrated inflammatory cell mediated NO production by iNOS (interstitial nitric oxide synthase pathway), resulting in high NO levels and toxic products that degrade elastin and disrupt the extracellular matrix.

Enhanced NO production has also been documented, via the iNOS pathway, following an increase in the local interstitial concentration of acetylcholine ***(Vanhoutte et al., 1989).***

Fukuda et al. (2000) and ***Johanning et al. (2001)*** have experimentally shown that NO production plays a major role in inflammation and aneurysm pathogenesis, and that inhibition of NO has been shown to limit aneurismal dilation of the aorta.

- ***Histopathology of ectatic arteries:***

Microscopic examination of atherosclerotic ectatic artery reveals thickened fibrotic intima with lipid deposition with foam cells and fibrous caps. There is a marked destruction and reduction of the medial elastic fibers with disruption of the internal elastic lamina, usually out of proportion to the degree of intimal involvement ***(Virmani et al., 1986).***

The functional loss of these components is the predominant pathology in CAE ***(Befeler et al., 1977)*** and possibly results from chronic vascular inflammation.

In the non-atherosclerotic forms of CAE, there is an intact vessel intima, but with extensive media degeneration, where smooth muscle is replaced by hyalinized collagen ***(Rath et al., 1985).***

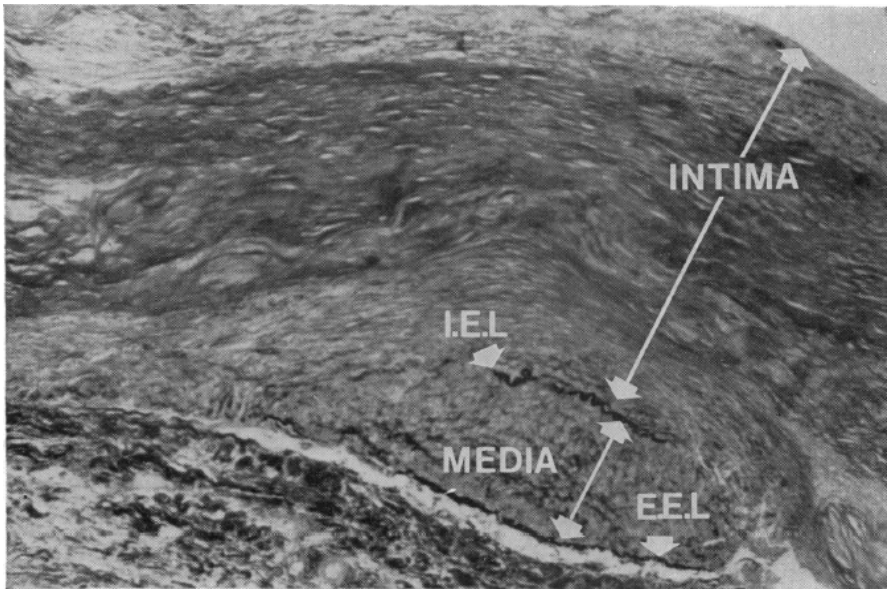


Fig. (4): Histology from ectatic coronary artery. Grossly thickened and fibrotic intima. Elastin of both internal and external elastic laminae degenerate. IEL, internal elastic lamina; EEL, external elastic lamina ***(Swanton et al., 1978)***

- ***Coronary ectasia in relation to cardiovascular risk factors:***

1) Gender:

Several studies have evaluated the traditional cardiovascular risk factors in patients with CAE as compared to those with CAD. ***Giannoglu et al., 2006*** reported a male dominance in patients with CAE. This gender difference was reported previously ***(Swanton et al., 1978)***, ***(Hartnell et al., 1985)*** and supposed to be due to the lower incidence of CAD in women, although the relation between CAE and CAD is not fully understood ***(Giannoglu et al., 2006).*** Moreover, the higher likelihood of males having CAE compared to women is