Flow Dynamics in Coronary Artery Ectasia Through assessment of Fractional Flow Reserve in patients with coronary artery ectasia

Thesis

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By

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Introduction

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)**.

The condition was first described by **Bourgon** in 1812 as a postmortem finding. 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)**.

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)**.

In CASS registry, CAE was found in 4.9% of more than 20000 coronary angiograms they reviewed **(Swaye et al., 1983)**.

The exact causative mechanisms of abnormal luminal dilation in CAE are essentially unknown, but evidence suggests a combination of genetic predisposition, common risk factors for CAD and abnormal vessel wall metabolism **(Manginas and Cokkinos, 2006)**.

The frequent coexistence of CAE with CAD and histopathological findings resembling those of atherosclerosis,

have led to the conclusion that the mechanism underlying the pathogenesis of CAE is a variant of atherosclerosis. However, there are some differences in the proven association with CAE compared to CAD indicating that the mechanisms underlying CAE might differ from the ones observed in atherosclerosis **(Yetkin and Waltenberger, 2007)**.

CAE has been classified according to their etiology into, CAE related to nitric oxide (NO) overstimulation and atherosclerotic origin of CAE in patients with concomitant CAD. These 2 groups constitute about 80-90% of all causes of CAE.

CAE has been found in association with both traditional and novel cardiovascular risk factors, the latter were found to have both diagnostic and prognostic implementations in the course of the disease **(Tokozoglu et al., 2004; Dagli et al., 2009)**.

CAE commonly presents with angina, rarely with ST elevation myocardial infarction or Non ST elevation myocardial infarction. Arrhythmias and sudden cardiac death were also reported **(Akyurek at al., 2003; Aboeata et al., 2012)**.

Disturbances in blood flow filling and washout are common, and are clearly associated with the severity of CAE. Angiographic signs of turbulent and stagnant flow include delayed antegrade dye filling, a segmental back flow phenomenon and local deposition of dye (stasis) in the dilated coronary segment **(Kruger et al., 1999)**.

There's a dispute regarding the appropriate management of patients with CAE where optimal treatment guidelines have not been established **(Ramappa et al., 2007)**.

Many methods can be used for assessment of the coronary flow e.g. Doppler wire, positive emission tomography, magnetic resonance imaging, thallium perfusion and transesophogeal echocardiography **(Strauer, 1990)**.

Akyurek et al. (2003) directly evaluated the slow flow in CAE using Doppler wire to measure blood flow velocity and coronary flow reserve (CFR) in patients with isolated CAE and reported a trend for lower resting blood flow velocity.

Fractional flow reserve (FFR) is the ratio of maximal myocardial blood flow depending on a stenotic artery to maximal myocardial blood flow if that same artery were to be normal. In other words, it is a fraction of the maximal normal flow, assuming that these measurements are obtained when the microvasculature resistance is minimal and constant (maximal hyperaemia) **(Puymirat et al., 2010)**.

FFR is a useful clinical tool for assessing the functional significance of coronary atherosclerosis. It might be of value in detection of the mechanism of ischemia in CAE **(Weon et al., 2003)**.

Aim of the work

This study aims at the assessment of flow pattern in major epicardial coronary arteries in patients with CAE through the assessment of FFR recordings at baseline and after injection of different hyperemic stimuli (Nitroglycerine, Adenosine, and Dipyridamole).

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 **(Figure 1).**

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.

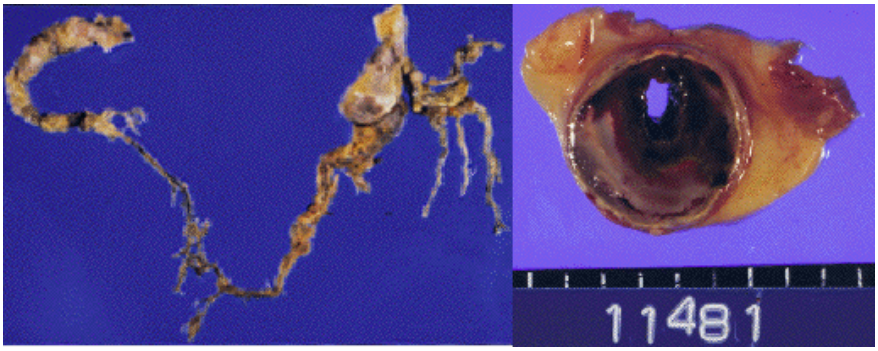


Figure (1): Coronary arteries obtained from autopsy sample **(Sorrell et al., 1996)**

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)**.

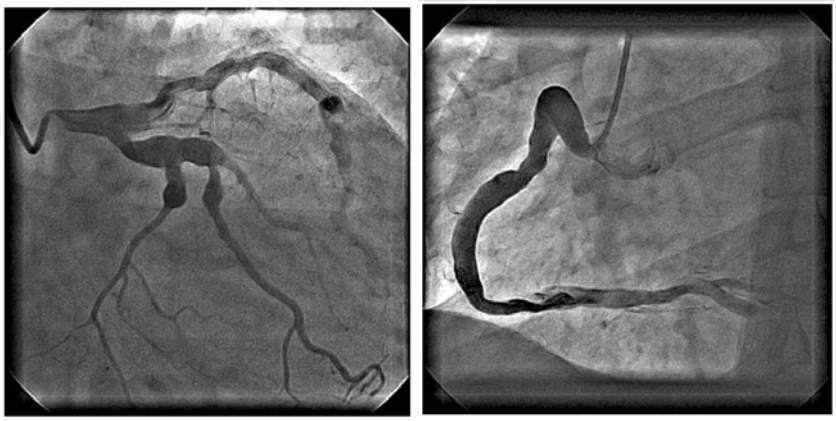
CAE may occur alone in a condition known as "dilated coronopathy" or in association with atherosclerotic CAD.

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

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) (Figure 2).**



(A) **(B)**

Figure (2): Different angiographic views showing: (A) Diffuse ectasia of LMCA, proximal LAD&LCX focal ectasia. (B) Diffuse RCA ectasia **(Helmy et al., 2009).**

Incidence of CAE:

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)**.

Since patients referred to coronary angiography are preselected, these incidences might overestimate the true frequency in general population **(Manginas and Cokkinos, 2006)**. On the other hand, as the distribution of CAE is quite variable, not always focal and normal reference segments may not be readily apparent, potential underestimation of the true incidence of the disease is evident. However, this might only be due to variations between different populations studied, observer bias, or random variations in small series **(Hartnell et al., 1985)**.

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 nonectatic 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)**.

Etiology and Pathogenesis:

The exact causative mechanisms of abnormal luminal dilation in CAE are essentially unknown, but evidence suggests a combination of genetic predisposition, common risk factors for CAD and abnormal vessel wall metabolism **(Manginas and Cokkinos, 2006)**.

CAE has been classified according to their etiology into, CAE related to NO overstimulation and atherosclerotic origin of CAE in patients with concomitant CAD. These 2 groups constitute about 80-90% of all causes of CAE.

Aboeata et al. in **(2012)** reviewed the current concepts of CAE and suggested that exaggerated positive vascular remodeling due to inflammation and chronic overstimulation of the endothelium by NO are potential causative mechanisms.

Other etiologies include congenital CAE and CAE related to connective tissue disorders (10-20% of all CAE causes).

Congenital CAE is frequently associated with other cardiac anomalies such as bicuspid aortic valve, aortic root dilatation, ventricular septal defect or pulmonary stenosis, and independent of any cardiovascular risk factors **(Seabra et al., 1974)**. It has also been well documented in patients with cyanotic congenital heart disease. The necropsy specimens of dilated and tortuous coronary arteries showed medial smooth muscle loss, increased medial collagen and disrupted internal elastic lamina **(Chugh et al., 2004)**.

The differentiation between congenital and acquired coronary aneurysms may often be difficult, despite the exclusion of other associated diseases **(Kruger et al., 1999)**. Acquired CAE should also be differentiated from coronary aneurysms following coronary interventions; coronary stent placement, atherectomy and brachytherapy **(Condado et al., 1997; Noguchi et al., 1999)**. Occasionally large ulcerated coronary plaques can be misinterpreted angiographically as coronary aneurysms. Their true cause can be usually revealed with intravascular ultrasound (IVUS) **(Ge et al., 1995)**.

Coronary dilatation has been described in association with connective tissue disorders such as scleroderma **(Chaithiraphan et al., 1973; Tarek et al., 2006)**, in Ehlers-Danlos syndrome **(Imahori et al., 1969)**, different types of antineutrophil cytoplasmic antibody (ANCA)-related vasculitis **(Mavrogeni et al., 2009)**, in syphilitic aortitis **(Morgagni, 1761)** and in Kawasaki disease **(Davidson et al., 1991)**.

Taking all findings, CAE occur, mainly due to two different mechanisms in two distinct patient groups: CAE due to NO overstimulation and CAE due to severe chronic inflammation.

Group I: CAE due to NO vascular overstimulation

Rarely, CAE occurs in subjects without coronary atherosclerosis as a result of exogenous interstitial NO vascular overstimulation.

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

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

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

Clustering of CAE has been observed in Vietnam veterans exposed to Agent Orange, the components of this chemical compound antagonize acetylcholinesterase, thus producing higher levels of acetylcholine and enhanced NO production suggesting a possible link between NO overstimulation and medial thinning leading to CAE **(England, 1981)**.

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 aneurysmal dilation of the aorta.

An association between peripheral varicose veins and CAE has been recently documented as the over expression of the iNOs has been shown in varicose veins together with an increased expression of tissue growth factor-1 (TGF-1) and the presence of macrophages **(Jacob et al., 2005)**.

CAE was suggested to be a diffuse disease associated with dilation in other vascular beds, probably owing to a common underlying pathogenic mechanism **(Aboeata et al., 2012)**.

Group II: CAE due to severe and chronic arterial inflammation

This is the most common type of CAE, and is almost always associated with stenotic CAD.

Though there's still a dispute about the etiologic mechanism of CAE, and why stenosis occurs in some vessels while ectasia occurs in others, or even in the history of a single atherosclerotic lesion, a phase of ectasia (or the so called positive remodeling) preceeds the formation of stenotic lesion (or the so called negative remodeling or arterial shrinkage), it has become clear that coronary atherosclerosis can no longer be thought of as a "fixed" model where plaque growth would always lead to luminal narrowing **(Libby, 2008; Glagov et al., 1987)**. A more accurate model would be that of "arterial remodeling" where coronary atherosclerosis may cause vessel obstruction or dilation **(Lam and Ho, 2004)**. In this way, the triad of atheroma, thrombosis, and aneurysm becomes linked in one continuous pathological process.

Normally in the process of development and maintenance of any artery, smooth muscle cells (SMCs) of the media produces the extracellular matrix (ECM), this biosynthesis is balanced by its breakdown mediated by the group of enzymes matrix metalloprotinases (MMPs) which, in turn, are under the regulation of their Tissue Inhibitor Metalloprotinases (TIMPs). **Lamblin et al. (2002)** focused on the system of MMPs which are actively involved in the proteolysis of ECM proteins, and found that MMP-3 5A/5A genotype was significantly more

frequent in patients with CAE, than in a control group of CAD patients. This over expression of MMP-3 gene possibly has a contribution to vascular remodeling as it leads to enhanced vessel wall degradation of various matrix proteins such as proteoglycans, laminin, fibronectin, collagen types III, IV, V, and IX with subsequent excessive vessel wall dilation.

These results are in line with recent evidence suggesting a critical imbalance between MMPs and their endogenous tissue inhibitors (TIMPs), as it has been demonstrated in patients with CAE **(Finkelstein et al., 2005)**. Additionally MMP-3 activity was found to be increased in the wall of aortic aneurysms **(Newman et al., 1994)**.

The role of angiotensin II in abnormal vascular remodeling was studied for its possible involvement with development of CAE. Experimental data suggest that activation of renin angiotensin system may lead to an increased inflammatory response in the vessel wall, alteration of SMC migration by inducing MMPs production, and stimulating reactive oxygen species formation. **Daugherty** and colleagues showed that angiotensin II infusion in apolipoprotein E deficient mice dramatically promoted vascular pathology, including an increase in the extent of atherosclerosis, a change in the nature of lesions and surrounding adventitial tissue, and formation of large aortic aneurysms **(Daugherty et al., 2000)**.

Gulec et al. (2003) suggested an association between ACE I/D (Angiotensin converting enzyme insertion/deletion)

polymorphism and the development of aneurysms where DD genotype was significantly more prevalent in patients with CAE (whether isolated or with concomitant CAD) compared to patients with significant stenotic CAD in absence of CAE. The correlation of DD genotype in CAE with concomitant CAD remained significant in comparison to patients with significant stenotic CAD even after eliminating patients with isolated CAE.

In a study by **Tokozoglu et al. (2004)**, inflammatory markers such as the plasma interleukin-6 (IL-6) and C-reactive protein (CRP) levels were found to be elevated in patients with CAE compared to those with normal coronaries. In accordance with these findings, **Turhan et al. (2004)** also reported an increased level of CRP and adhesion molecules indicating an increased inflammatory process in patients with isolated CAE compared with both patients with and patients without CAD.

Yetkin and Waltenberger (2007) postulated that cytokine induced tissue inflammation is an underlying contributor for vascular remodeling.

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 the pathogensis of CAE.