Coronary Artery Ectasia; Clinical Updates and Management Options in Acute Presentation

Authors

Richard Tanner MD

Santhosh David MD

Ronan Conlon MD

Usama Boles MD

Authors Note

Departement of Cardiology,

Letterkenny University Hospital,

Letterkenny, Ireland

No conflict of interest to declare

Corresponding Author;

Dr Usama Boles MRCPI, MSc, FESC

Consultant Cardiology

Cardiology Departement,

Letterkenny University Hospital

Email: bolesu@tcd.ie

Telephone: 00353 74 912 5888, ext 2828

Fax; 00353 74 912 5888

Abstract

Coronary artery ectasia (CAE) is defined as dilatation of an arterial segment to a diameter at least 1.5 times that of an adjacent normal coronary artery and involves more than one third of the legnth of the artery.(1) CAE has been observed in 3-8% of patients undergoing coronary angiography and 1.4% of autopsy series.(2) A lower incidencewas reported in a more recent study, which may reflect strict adherence to diagnostic criteria and geographical variation.(3)CAE has a male predominance (1.7% compared to 0.2%) anda predilection for the right coronary artery.(1)There has been conflicting data on the pathogenesis of CAE to date.(1, 2, 4) In contrast to earlier research, more recent studies have suggested that CAE is non-atherosclerotic in nature.(4, 5)Understanding the true pathogenesis is essential to assessing patient cardiovascular risk and optimizing individualised patient treatment.

Aetiology

The exact aetiology of CAE is not well defined. It is attributed to atherosclerosis in 50% of cases. It is thought that CAE represents an exaggerated form of extensive vascular remodelling in response to atherosclerotic plaque growth with extracellular enzymatic degradation playing a major role in ectatic vessel formation.(6, 7)Furthermore, the in vivo experience with intra-vascular ultrasound (IVUS) has confirmed that both arterial expansion and shrinkage can be a manifestation of coronary atherosclerosis. Atherosclerotic lesions within ectatic regions of the coronary arteries tend to be highly inflamed, high-risk plaques with a propensity to rupture.(7)

Up to 20-30% of cases are considered congenital and 10% to20% of cases areassociation with inflammatory or connective tissue diseases, e.g. Ehlers- Danlos, Kawasaki, polycystic kidney disease. (1) Studies have reported the incidence of coronary aneurysms after balloon angioplasty at 0.3% to 4%, with a higher incidence (9%) when the angioplasty was complicated by dissection. (8, 9) In the absence of the above aetiologies it may be described as idiopathic CAE.

Pathogenesis

The underlying pathogenesis of CAE is not well understood. Histologically, CAE has many similar vessel wall feature to coronary artery disease; hyalinization and lipid deposition of the intima, destruction of the intima and media, focal calcification and fibrosis,(2) The loss of the musculo-elastic arterial wall seems to be a unique characteristic for CAE and this change results in marked attenuation of the vessel wall and dilatation. (10)The essential component in the formation of coronary aneurysm is thought to be an abnormal vessel media which may be secondary to an extension of the intimal arteriosclerotic process. (11) However, it is becoming increasingly recognised that traditional cardiovascular risk factorsare not the only contributors to CAE formation. This is supported by the histological variance and a paradoxical low prevalence of CAE in diabetics. (4)Furthermore, those with pure CAE have been found to be younger, have diffuse disease involving the 3coronary branchesand have less traditional cardiovascular risk factors than those with mixed CAE and CAE.(4) Hence, it appears inappropriate to label CAE as a variant of atherosclerosis. CAE have been found to have over-expression of matrix metalloproteinase (MMP), which contributes to excessive vessel dilatation and aneurysm formation. Interestingly this is down-regulated in diabetes and may explain the lower incidence of CAE in diabetics.(5)

Morphological classification of CAE

While coronary angiography is the main diagnostic technique for the identification of coronary artery ectasia, IVUS is required for determining CAE morphology.(6)The Markis Classification is often used: Type 1: diffuse ectasia of two or 3 vessels, Type 2: diffuse disease in one vessel only and localised disease in another vessel, Type 3: diffuse ectasia of one blood vessel, Type 4: localised or segmental ectasia. (10) It has been proposed that the term aneurysm be restricted to a localised, abnormal dilatation of a coronary artery which can be saccular or fusiform in shape, while reserving the term ectasia to describe diffuse dilatation only (at least a 3 third of the artery).(12)Adherence to this clear definition is needed to allow accurate estimation of CAE prevalence and to facilitate comparison between different CAE studies.

Biochemical markers

The role of biomarkers in detecting CAE remains unclear. The ideal biomarker would help differentiate CAE from obstructive atherosclerosis and normal coronaries. A number of biomarkers have been proposed, see Table 1. Inflammatory markers such as white cell count,C-reactive protein and interleukin-6 are often elevated in those with CAE. (13)Plasma soluble adhesion molecules such as Intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-Selectincan be raised in patients with CAE without obstructive coronary artery disease (CAD) in comparison to patients with CAE with obstructive coronary artery disease and those with normal coronary arteries. (14) It has been suggested that an imbalance

betweenmatrix-metalloproteinase and tissue inhibitors of metalloproteinase (TIMP)may contribute to ectatic formation.(15) The neutrophil tolyphocyte ratio has been found to be higher in those with isolated CAE and those with CAD compared to those with angiographically normal coronary arteries.(16)

Table 1: Inflammatory markers in Coronary Artery Ectasia

Author	Year	Markers	Sub-groups in study	Conclusion
Li JJ (13)	2009	- Cytokines -Blood cell count	- 55 patients with isolated CAE - 38 patients withobstructive CAD -33 patients with angiographically normal coronaries	WCC, CRP & IL-6 raised in CAE compared to obstructive CAD and those with normal coronaries.
Turhan H(14)	2005	-Plasma soluble adhesion molecules	- 32 patients with isolated CAE without stenosis - 32 patient with obstructive CAD without CAE - 30 patients withnormal coronary arteries	Isolated CAE associated with raised ICAM-1, VCAM-1, E-Selectin
Dogan A (17)	2008	- Matrix metalloproteinases - Interleukins - Inflammatory markers	- 28 patients with CAE - 27 patients with CAD - 22 patients with angiographically normal coronaries	MMP-3, MMP-9, and IL-6 may be responsible for ectasia formation in patients with CAE. hsCRP similar in all three groups
DaoudEM (18)	2012	-Plasma soluble adhesion molecules	- 16patients with isolated CAE - 16 patients with obstructive CAD - 10 patients with angiographically normal coronaries	ICAM -1 significantly higher is isolated CAE. No significant difference in E-Selectin between groups
Adiloglu AK (19)	2005	- Interleukins - Inflammatory markers	- 88 patients with 3 or more obstructed vessels - 65 patients with CAE without atherosclerosis - 91 patients with angiographically normal vessels	hsCRP significantly higher in CAE compared to controls. IL-6 higher in CAD compared to controls
Yilmaz H(20)	2006	- Adhesion molecules	- isolated CAE without CAD - obstructive CAD and CAE - obstructive CAD without CAE - normal coronary arteries	Significantly increased ICAM-1 and VCAM-1 in patients with CAE and those with obstructive CAD with CAE.
Turhan H (21)	2004	-Inflammatory markers	- 32 patients with isolated CAE - 32 patients with CAD without CAE - 30 patients with angiographically normal coronaries	CRP significantly higher in those with isolated CAE
Finkelstein A(15)	2005	-Matrix metalloproteinases - Inflammatory	- 34 patients with isolated CAE - 26 patients with CAD without CAE - 27 patients with angiographicallynormal	Serum levels of MMP-2, MMP-3, TIMP-1, proBNP and

		markers	coronaries	hsCRP did not differ between the three groups.

CAD- coronary artery disease, CAE – coronary artery ectasia, WCC- white cell count, hsCRP – high sensitivity c-reactive protein, IL-interleukin, ICAM – Intracellular adhesion molecule, VCAM – vascular cell adhesion protein, MMP – matrix metalloproteinase, TIMP - tissue inhibitors of metalloproteinase, proBNP – N-Terminal pro b-type natriuretic peptide

Electrocardiogram findings in CAE

Few studies have analysed the Electrocardiogram (ECG) changes in patients with CAE. One small study (n=20) found that isolated CAE was associated with prolonged dispersion of P-wave and QT interval.(22) A more recent study assessed theTp-Te (interval between the peak and end of the T-Wave) and Tp-Te/QT interval in those with CAE.(23) Tp-Te is accepted as an index of transmural dispersion of ventricular repolarisation. Myocardial repolarisation is associated with susceptibility to ventricular tachy-arrhythmias. Thus, Tp-Te ratio and Tp-Te/QTc ratio can be used as an electrocardiographic index of ventricular arrhythmogenesis. This study found that patients with CAE had significantly higher values of Tp-Te and Tp-Te/QT than those with normal coronary arteries. Hence, they concluded that that those with CAE may carry an increased arrhythmogenesis risk.(23) Increased Tp-Te interval and Tp-Te/QTc ratio has also been found in those with isolated coronary slow flow, a phenomenon which is often associated with CAE.(24) Further studies are required to examine if these findings extrapolate to larger populations with CAE.

Coronary slow flow

The presence of aneurismal segments produces sluggish and turbulent blood flow. This is associated with an increased incidence of typical exercise induced angina pectoris and myocardial infarction, regardless of the severity of co-existing stenotic lesions. (6) Coronary slow flow (CSF) is characterised by protracted distal vessel opacification in the absence of significant epicardial CAD.TIMI frame count method (TFC), which is an index of coronary flow velocity along the entire coronary artery, can be used to assess CSF. CAE is associated with a higher TFC. (25) It has been found that while volumetric coronary blood flow is significantly higher in CAE, the average peak velocities of coronary blood flow during hyperaemia is significantly lower compared to those with normal coronary arteries.(26)Coronary flow reserve also appears to be reduced in those with CAE and this has led to thesuggestion that microcirculatory dysfunction may cause exercise induced ischaemia.(26)

Myocardial infarction in CAE

The guideline recommendations for patients presenting with ST elevation myocardial infarction (STEMI) with ectatic infarct-related coronary artery are the same as a STEMI in the absence of CAE. (27)A recent study from Melbourne found that patients presenting with a STEMI due to ectatic infarct-related artery (EIFA) were more likely to have a large thrombus burden (96% v's 22%), increased usage of glycoprotein IIb/IIIa inhibitors(GPI) (73% v's 37%) and greater post procedural anticoagulation use (28% v's 5%). Increased bleeding rates were not observed despite the increased use of GPI.(28) Patients with concomitant CAD and CAE have higher no-reflow rates and lower TIMI flow grades after percutaneous intervention. (28-30)Overall, despite high-burden thrombus formation and lower rates of successful reperfusion long term survival tends to be good.(31)

The presence of CAE in acute coronary syndrome (ACS) makes stenting more arduous. Challenges include optimal stent sizing, stent misplacement, stent embolisation and acute or sub-acute stent thrombosis.(32) In one study 44% of patients who presented with a STEMI and concomitant CAE did not receive a stent. The authors of this study attributed this to large vessel size, the persistence of large thrombus burden even after thrombus aspiration and initiation of GPI.(28) Low rates on stenting have been noted in previous studies.(33) There are no clear recommendations on the optimal stent to use in CAE with ACS. A randomised controlled trial has assessed the use of

everolimus-eluting, sirolimus-eluting and bare metal stents in patients requiring stents 3.0mm or more in diameter. This study found lower rates of target revascularisation with the drug eluting stents but no significant difference between the rates of death and myocardial infarction in those receiving drug eluting stents compared to bare metal stents.(34)

Intervention versus medical treatment

Guidelines on appropriate treatment for CAE do not exist. Evidence to date is from case reports and studies limited by population size, see table 2. Older studies recommended the use of long-term anti-coagulation based on significant flow disturbances within the ectatic segments, however this is controversial.(35-37) The European Society of Cardiology notes that chronic anticoagulation has not been prospectively tested and hence cannot be recommended until supported by subsequent studies. Anti-platelet agents are given to the majority of patients, as there is a high prevalence of co-existingobstructive CAD.The increased platelet activation in isolated CAE (unregulated P-selectin, beta-thromboglobulin and platelet factor 4) further supports the use of anti-platelet agents in CAE. (38) In contrast to obstructive CADthe use of nitrates is generally discouraged. Nitrates maycause further coronary epicardial dilation which can exacerbate myocardial ischaemia.(39) Statins may have an additional role in CAE as they can inhibit the secretion of metalloproteinase.(40) Losartan has been demonstrated to prevent the development of aortic aneurysms in a mouse model of Marfans syndrome (inhibition of TGF-b) and hence may have an indication in CAE.(40)

Percutaneous or surgical intervention is often used when symptoms fail to respond to medical treatment. A small study form 1990 found that patients undergoing angioplasty for lesions adjacent to an aneurismal coronary artery segment had similar outcomes to those with obstructive CAD without CAE. (41)Patients who present with a STEMI due to an ectatic infarct–related artery (EIRA) have a better in hospital prognosis if PCI is performed.(28)A number of surgical procedures have been used to treat CAE with or without co-existing obstructive CAD. While the most common procedure is coronary artery bypass grafting, proximal and distal ligation and aneurysm resection have been used to remove large aneurysms and treat thrombus formation within the CAE segment.(42)

Table 2

Treatment options in Coronary Artery Ectasia

Author	Year	Study details	Conclusion
Swanton RH (36)	1978	1000 angiograms 12 had CAE	Anticoagulation recommended
Sorrell VL(35)	1996	Review	Anticoagulation recommended
Demopoulous VP (37)	1997	Group A - 172 with CAE & CAD Group B - 31 with isolated CAE Group C - 165 with CAD without CAE	No additional risk in CAD with concurrent CAE. Use of anticoagulants should be questioned.
Sorrell VL (43)	1998	Review	Wafarin, aspirin and diltiazem recommended
Shanmugam BV (28)	2017	1834 primary PCI patients - 25 had EIRA - 1809 had non-EIRA	Improved in-hospital outcomes if PCI performed. High frequency of unstable angina and non-fatal MIs in both groups after discharge

CAE – coronary artery ectasia, PCI- percutaneous intervention, EIRA – ectatic infarct related artery, MI – myocardial infarct

Outcomes in CAE

Outcome data for those with CAE is limited to small studies. Overall isolated CAE seems to have a similar prognosis than obstructive CAD. (3, 44, 45)One of the largest studieson CAE follow up included 92 patients with CAE and compared this group to 114 patients with significant CAD without ectasia over a 30 month period.(3) This study found that although the incidence of unstable angina was higher in those with isolated CAE ($p<0.001$),the incidence of myocardial infarction ($p = 0.72$) and cardiac death ($p = 0.93$) did not differ significantly. The same study found the incidence of PCI to be lower in isolated CAE ($p< 0.001$) whereas the incidence of CABG was marginally higher ($p=0.13$) compared to those with significant CAD without ectasia.(3)However, it appears that patients who have a STEMI due to an ectatic infarct-related artery (EIRA) carry worse long term outcomes than those with non-EIRA.(28)Other factors associated with a poor prognosis include high thrombus burden which can lead to poor reflow after intervention.(31)

Conclusion

There is increasing evidence that CAE pathogenesis is not related to atherosclerosis, even though these two conditions often co-exist. The suggested inherent arrhythmogenic effect of CAE should be considered when evaluating patients, although further studies are required to gain a better understanding of the true arrhythmogenic risk associated with CAE. The findings of coronary slow flow and often high thrombus burden suggest that anticoagulation with Warfarin should be given consideration, especially in CAE without concomitant CAD. Finally, comparable short term outcomes have been observed between those with CAE and those without CAE undergoing primary percutaneous intervention. CAE has a quite challenging outcome in the first month of acute coronary syndrome , this propably related to a stagnant coronary flow and high coagulation tendency and burden in the coronaries. This may suggest a quite aggressive anticoagulation protocoles in such patients in addition to a standard management.

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