

Coronary artery ectasia as a culprit for acute myocardial infarction: review of pathophysiology and management

Koroner arter ektazisi akut miyokart enfarktüsünde sorumlu: Patofizyoloji ve yönetim derlemesi

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ABSTRACT

Coronary artery ectasia (CAE) is defined as localized coronary dilatation, which exceeds the diameter of normal adjacent segments or the diameter of the patient's largest coronary vessel by 1.5 times. The pathophysiology of CAE remains unclear as its relationship with atherosclerosis remains only modestly established. The histological variances and conflicting reports of the role of traditional cardiovascular risk factors, also, weakens the significance of such association. The slow coronary flow (CSF) of CAE may lead to ischemic and thrombotic events, a mechanism that has never been fully elucidated, but may play a fundamental role in its pathogenesis. While pure, non-atherosclerotic, CAE is believed to have better prognosis when compared to atherosclerotic obstructive CAE, it is thought that CAE is not a simple condition but rather has an adverse clinical course. Nevertheless, long-term prognosis and outcome of CAE is similar to atherosclerotic-non-CAE. Since CAE was first described, oral anticoagulants have been considered as a valid treatment option. Dual antiplatelet therapy is widely employed in acute coronary syndrome (ACS), which also applies to CAE patients presenting with ACS. However, there is a significant uncertainty about the best treatment strategy for CAE in acute myocardial infarction. We hereby report a variety of presentations of CAE complicated with ST elevation myocardial infarction (STEMI). Pathophysiological and anatomical varieties of ectatic coronary culprit lesions represent clinical challenges in uniformly managing this condition. Our review is unique in critically showing the pathophysiology, available controversial evidence upon management and prognostic features of CAE with STEMI. (*Anadolu Kardiyol Derg 2013; 13: 695-701*)

Key words: Coronary artery ectasia, acute myocardial infarction, oral anticoagulants, dual antiplatelet therapy, coronary slow flow

ÖZET

Koroner arter ektazisi (KAE) normal komşu segmentlerin çapını ya da hastanın en büyük koroner damarının çapını 1,5 kat aşan lokalize koroner genişlemesi olarak tanımlanır. Ateroskleroz ile ilişkisi sadece orta derecede kalacak şekilde kurulması gibi KAE'nin patofizyolojisi belirsizliğini korumaktadır. Histolojik farklar ve geleneksel kardiyovasküler risk faktörlerinin çelişkili raporlardaki rolü de böyle bir ilişkinin önemini azaltır. KAE'nin yavaş koroner akımı iskemik ve trombotik olaylara sebebiyet verebilir, mekanizma hiçbir zaman tam olarak açığa kavuşturulamamış olsa da, patogeneizde temel bir rol oynayabilir. Saf ve aterosklerotik olmayan KAE'nin aterosklerotik obstrüktif KAE ile mukayesede daha iyi bir prognozu olduğuna inanılırken, KAE'nin basit bir durumdan ziyade olumsuz bir klinik seyrinin olduğu düşünülüyor. Bununla beraber KAE'nin uzun dönem prognoz ve sonuçları aterosklerotik-KAE olmayana benzerdir. KAE ilk tanımlandığı günden bu yana, oral antikoagülanlar geçerli bir tedavi seçeneği olarak kabul edilmiştir. Akut koroner sendrom (AKS) için yaygın bir şekilde kullanılan ikili antiplatelet tedavi, AKS tablosu ile gelen KAE hastaları için de geçerlidir. Ancak, akut miyokart enfarktüsü KAE için en iyi tedavi stratejisi hakkında önemli bir belirsizlik bulunmaktadır. Burada, ST yükselmeli miyokart enfarktüsü (STEMI) ile komplike olan değişik KAE tablolarını rapor ediyoruz. Ektatik koroner sorumlu lezyonların patofizyolojik ve anatomik farklılıkları bu durumun tekdüze bir yönetiminde klinik güçlükler oluşturur. İncelememiz STEMI'li KAE'nin takip ve prognostik tablolarına bağlı zıt bulguların mevcudiyetinde, patofizyolojisi dikkatle incelemekte benzersizdir. (*Anadolu Kardiyol Derg 2013; 13: 695-701*)

Anahtar kelimeler: Koroner arter ektazisi, akut miyokart enfarktüsü, oral antikoagülan, çift antiplatelet terapisi, koroner yavaş akım

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Introduction

Coronary artery ectasia (CAE) is the abnormal dilatation of coronary arteries such that the ectatic segment exceeds the diameter of the normal adjacent segments or the diameter of the patient's largest coronary vessel by 1.5 times. CAE may be diffuse or segmental and in approximately 20-30% of patients is believed to be congenital in origin. The pathophysiology of CAE remains unclear.

Despite the close relationship between CAE and atherosclerosis, especially in the West, the histological variances and conflicting reports of the role of traditional cardiovascular risk factors weakens the significance of such association (1). CAE was first described over 40 years ago in association with atherosclerosis, since then anticoagulants have been considered as a treatment option (2) but this remains controversial.

Demopoulos et al. (3) reported better prognosis of pure, non-atherosclerotic CAE compared to atherosclerotic obstructive CAE. That was contradicted by the Japanese group (4), who claimed that CAE is not a simple condition but has adverse clinical course (5). Aside from a direct relationship between CAE and atherosclerosis, the risk of slow flow phenomenon and CAE described first by Markis et al. (6) may lead to ischemia and thrombosis but this mechanism has never been fully elucidated (7). Such variety of mechanisms and pathophysiology create significant uncertainty as to the best treatment strategy for patients with CAE in order to minimize potential complications.

We report three cases of CAE presented with ST elevation myocardial infarction (STEMI), which demonstrate various presentations and clinical challenges that exist when managing this condition. That review is unique in presenting the available controversial evidence for management strategies.

Case 1

A 70-year-old man with no prior medical history presented with inferior STEMI, based on an acutely recorded electrocardiogram (ECG) by the attending paramedics. ST segment elevation had resolved on patients' arrival to the Heart Center. He underwent a coronary angiogram which revealed diffuse CAE involving the proximal left circumflex and mid right coronary artery (RCA). Subsequently, percutaneous coronary intervention (PCI) was performed to the culprit atheromatous lesion of the mid RCA, using a clot aspiration device but with no success. A stent deployment using a challenging high pressure-endurance balloon to overcome the well-organized atheroma and thrombus was needed and gave good final results (Fig. 1).

Case 2

A 55-year-old man developed severe exertional chest tightness. A resting ECG showed left bundle branch block so he underwent urgent coronary angiography, which demonstrated diffusely ectatic coronary arteries with minor atherosclerosis. However, it was noted that there was slow flow and stagnation of the contrast in some of the ectatic segments in the absence

of any flow obstructing lesions (Fig. 2). No coronary intervention was required. Cardiac markers rose and the patient was treated as STEMI. The patient was discharged on beta-blocker, statin, aspirin and glycoprotein II inhibitor. Warfarin was discussed as an option for treatment, but the priority was given to dual antiplatelet to treat as conventional MI.

Case 3

A 64-year-old lady presented with inferior STEMI. There was a big thrombus burden within CAE segment in proximal RCA. That was the culprit lesion, which was eventually treated by a drug eluting stent. A week later, intravascular ultrasound (IVUS) revealed a clot beneath the stent in the ectatic area with no evidence of atherosclerosis (Fig. 3). The patient was discharged on dual antiplatelet therapy. Oral anticoagulation was added in view of the spontaneous thrombus formation. Clopidogrel was stopped after 6 weeks and she remained on long-term Aspirin and oral anticoagulation.

Discussion

Pathogenesis of coronary artery ectasia

Studies of coronary arterial wall pathology highlighted the lack of uniformity in CAE. In patients with mixed CAE, Swanton et al. (8) reported similar histological appearance to that of atherosclerosis with marked destruction and reduction of the medial elastic fibers with disruption of the internal and external elastic laminate. On the other hand, the pure form of CAE showed smooth muscle hyalinization of the coronary fibro-muscular media leaving the intima intact (9). This finding were taken further by Fukuda et al. (10) and Johanning et al. (11) who related the hyalinization process to excessive nitric oxide (NO) production. This was supported by reports in the early 1980s, which investigated the association between CAE and excessive herbicide exposure. The herbicides themselves were shown to increase nitric oxide production that leads to hyalinization by indirect acetylcholine production (12).

Congenital CAE as part of systemic arteriopathy

CAE has been shown to be associated with similar aneurysm formation in other parts of the arterial tree including abdominal aorta and peripheral arteries, hence the suggestion that ectasia may represents a generalized deficit of the wall of the entire arterial system (13). The congenital type of CAE is associated with other anomalies like bicuspid aortic valve, aortic root dilatation and aneurysms (14), pulmonary stenosis and ventricular septal defect (20, 15). Similar association between CAE and lower limb venous varicosities has also been suggested but with limited supportive evidence (16).

Kawasaki disease (KD): It is one of the most common causes of acquired heart disease in children, causing CAE in 15-25% of affected cases. Geographical distribution of Kawasaki disease also determines the prevalence of potential coronary complica-

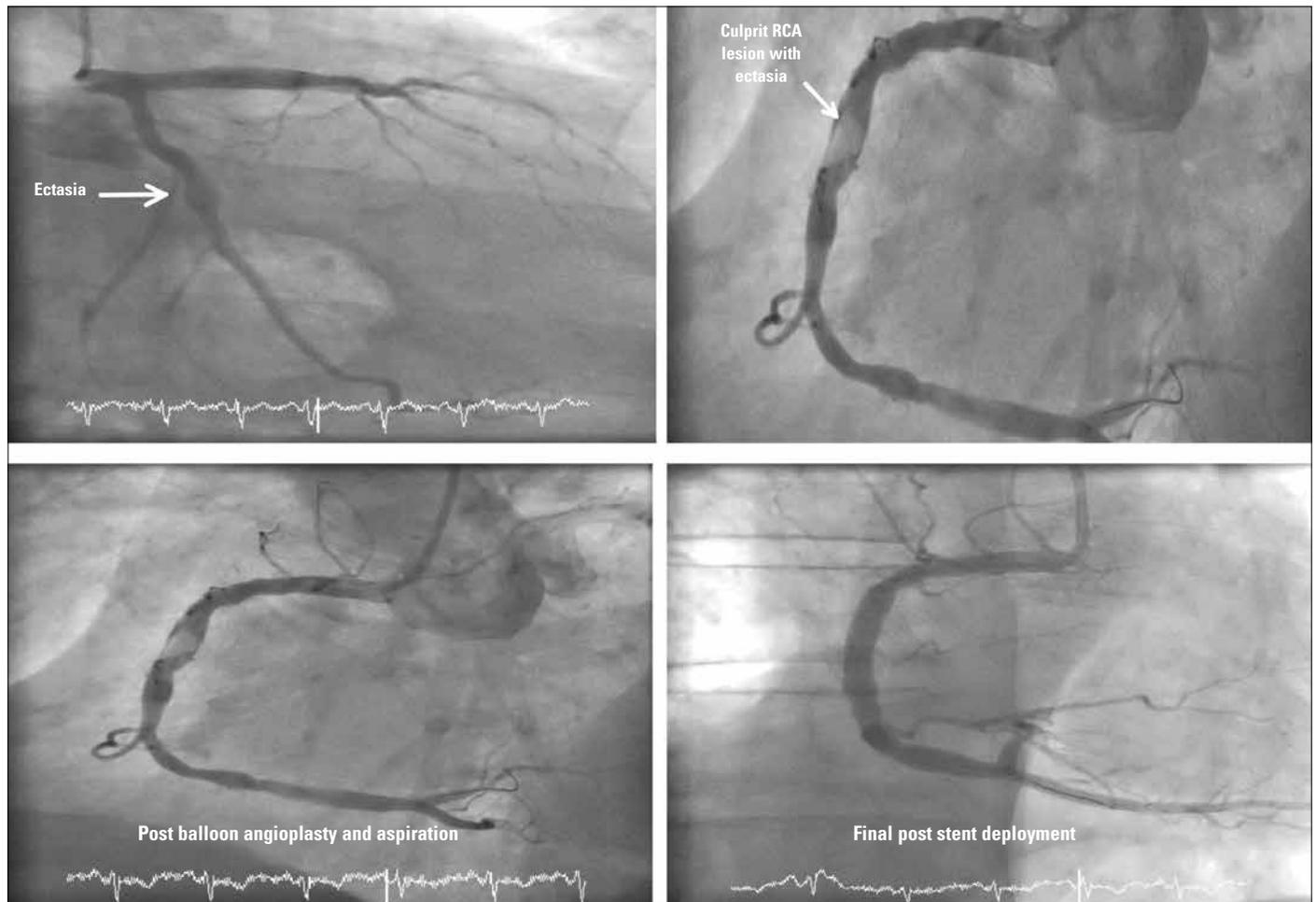


Figure 1. Culprit lesion in ectatic RCA before and after angioplasty

CAE - coronary artery ectasia, RCA- right coronary artery



Figure 2. Demonstrating coronary slow flow in coronary artery ectasia

LAD - left anterior descending artery, LCX - left circumflex artery

tions, affecting 19 out of 100.000 children in USA compared to 174 out of 100.000 kids under 5 years age in Japan (17). Despite being linked with coronary artery disease (CAD), KD remains more commonly seen in Japan and East Asia than in the West.

Takayasu arteritis (TA) is a syndrome of chronic pan-arteritis, with rare coronary involvement, with annual incidence of 2.6 per million (18). In one large study (1961 to 1989) in patients with TA and angina; coronary ostial disease was found in 73%, proximal CAD, 17%, left main ostial lesions representing 67%, with more than 90% occlusion or even total occlusion (19).

Idiopathic CAE might be seen in other forms of much rare arteritis e.g. syphilitic.

CAE and arterial remodeling

Another pathological explanation for CAE is remodeling, which was first described by Glagove et al. (20). His theory was based on the finding that early compensatory enlargement of human atherosclerotic coronary arteries occurs even before noticeable luminal narrowing, simulating CAE appearance. This arterial enlargement occurs mainly in the

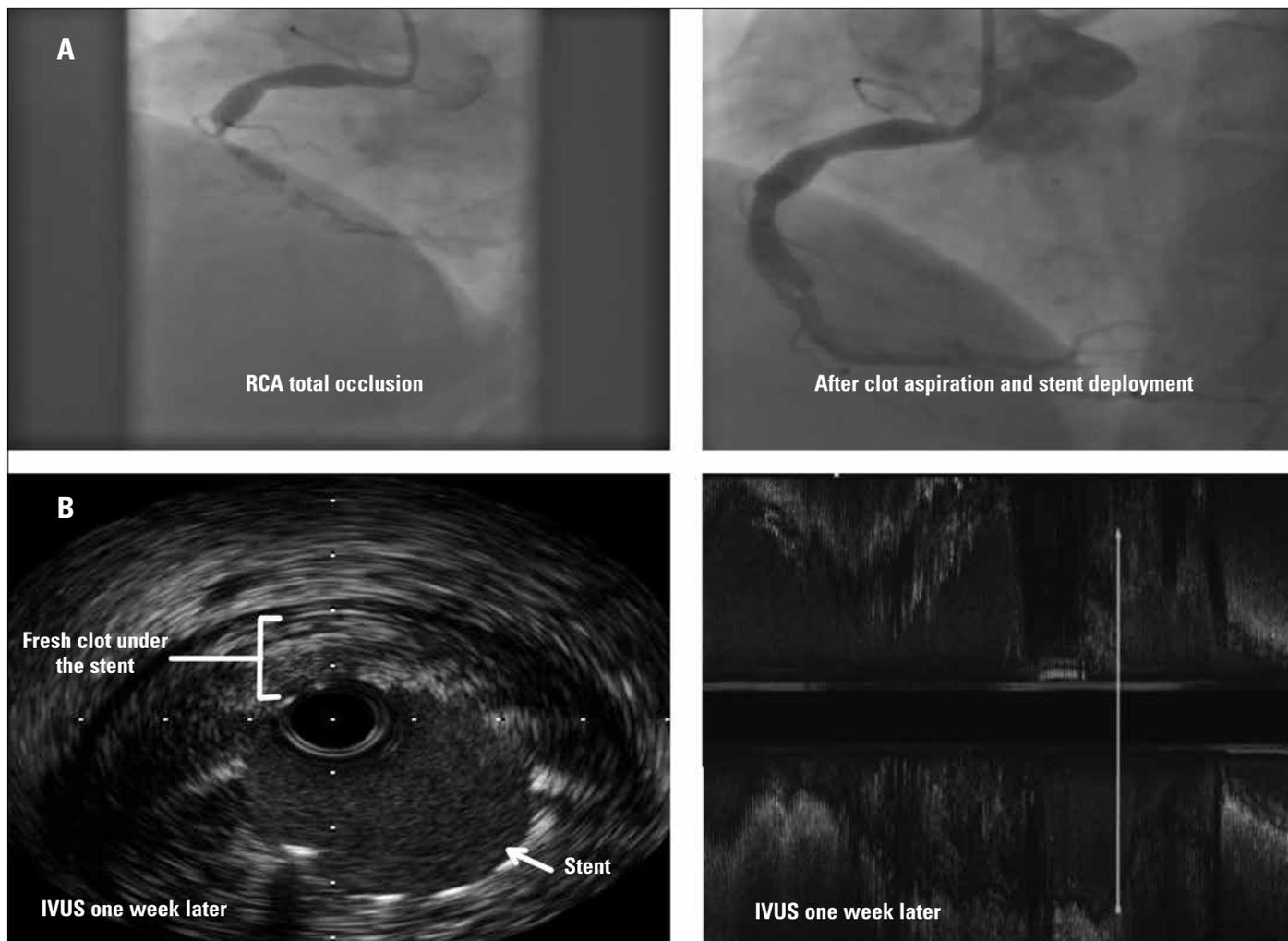


Figure 3. A- coronary angiography revealing subtotal RCA occlusion pre and post-intervention B- intravascular ultrasound (IVUS) of the RCA one week after PCI showing thrombus underneath stent struts.

PCI - percutaneous coronary intervention, RCA - right coronary artery

external elastic lamina with positive adaptation of the internal elastic lamina giving a false impression of patent coronary lumens with or without minimal atherosclerosis (21). This mechanism suggests a risk for arterial wall vulnerability with potential progress to acute coronary syndrome. In contrast, negative remodeling of coronary inner elastic lamina is expected to have a more benign and stable prognosis and also it appears earlier in the lumen, alarming for a better disease control (22). Although these theories appear reasonably sound, they are unable to explain many of the features that distinguish CAE from atherosclerosis. That explanation of coronary remodeling is vague and difficult to explain based on the current knowledge.

CAE and inflammatory biomarkers

The literature data failed to provide a pathognomonic biomarker for CAE; the ones quoted are known to be already abnormal in atherosclerosis and consequently would explain the same inflammatory response, with some markers quite higher in

CAE than in atherosclerosis. Conventional inflammatory markers like cytokines, tumor necrosis factor (TNF) and interleukin 6 (are generally good markers for systemic inflammation, and have been found to be elevated in 50% of CAE patients, particularly in those with evidence for atherosclerosis (23) but have failed to differentiate between the two conditions. On the other hand, markers like inflammatory cells e.g. leucocytes count; monocyte count and C-reactive protein are closely linked to the presence of CAE, although not specific (24). Furthermore, soluble adhesion molecules (e.g. ICAM and VCAM) were also found to be higher in isolated CAE as well as in CAE with occlusive CAD compared with occlusive coronaries without CAE. These findings suggest that more severe coronary wall inflammation may play a role in CAE pathogenesis (25).

Clinical challenges in coronary artery ectasia

Coronary slow flow (CSF): This angiographic phenomenon is frequently referred to as a potential mechanism for explaining angina in CAE in the absence of flow limiting lesions. CSF is

characterized by delayed distal vessel opacification in the absence of significant epicardial coronary artery disease. CSF was reported in a number of cases and has been shown to predispose patients to myocardial ischemia, even myocardial injury, during stress particularly in those with diffuse disease (26, 27). CSF can be assessed by the TIMI frame count method (TFC), an index of coronary flow velocity along the entire epicardial coronary artery. CAE is usually associated with a higher TFC (slower flow) (28). Magnetic resonance based peak flow velocity (PFV) is another method for assessing CSF which carries the advantage of being non-invasive (29). In view of this finding, the exercise related ischemia in CAE could be explained on the basis of a volumetric discrepancy between epicardial and peripheral microcirculatory vessels (30). However, CSF could be seen in the ectatic segment which seems out of proportion with the increased diameter, but still not easy to interpret in routine clinical practice.

CAE, slow coronary flow and endothelial dysfunction

A distinct morphological pattern of CAE is the aneurysmal dilatation and slow flow, which causes angina, in the absence of any flow limiting lesions. This was thought to be related to coronary endothelial dysfunction, assessed by plasma asymmetric dimethyl arginine (ADMA) levels and endothelium-dependent flow-mediated dilatation (FMD), having excluded the inflammatory response as a potential contributor (31). Ackay et al. (32) found a direct relationship between CAE and erectile dysfunction suggesting that endothelial dysfunction in CAE may manifest in two different forms, thus adding to the already existing pathophysiological confusion.

Pre-infarction angina (PA)

This phenomenon has beneficial effects attributed to the development of ischemic preconditioning (with more collateralization of the microcirculation) resulting in reduced infarct size in patients with acute myocardial infarction receiving thrombolysis (33). PA has better prognosis in CAE patients treated by primary angioplasty (34). Patients with atherosclerotic CAE and PA have been shown to achieve an equally good outcome when treated with primary PCI compared to atherosclerotic CAD with PA (35). However, further details on culprit lesions (CAE related), extent of disease, and coronary anatomy should assist in better differentiation between CAE and CAD and hence strategic management plans.

Mean platelet volume (MPV)

MPV is a measurement of the average size of platelets and is typically included in blood tests as part of the CBC. MPV is higher when there is destruction to platelets when the body is producing increased number. A typical range of platelet volumes is 9.7-12.8 fL, is associated with major adverse cardiac events including nonfatal myocardial infarction and even cardiac death (36). High MPV is another marker for thrombosis in CAE, having

been found to be higher in CAE compared to atheromatous CAD, hence suggested as a potential follow-up marker in CAE, irrespective of CAD (21). In addition to MPV, patients with pure CAE (non stenotic) have been found to have abnormally raised plasma P-selection, beta-TG and PF4, suggesting increased platelet activation and higher tendency to thrombosis (37).

Thrombus burden

TIMI frame count measurement has been found to be significantly higher in CAE and well correlated with ectatic segment size and ratio (38-40). This suggested a clear predisposition to higher thrombus burden in the ectatic segments and adverse outcome. Erden et al. (39) found impaired epicardial arterial flow, thrombus burden score of infarct-related artery (IRA), impaired TIMI Myocardial Perfusion Grade, and distal embolization significantly higher and ST-segment resolution and collateral vascular development significantly lower in infarct related CAE. Prior to these findings, Yip et al. (40) had also found that ectasia related infarct is associated with high-burden thrombus formation and has a significantly lower incidence of successful reperfusion (38).

Myocardial performance index (MPI)

MPI incorporates both systolic and diastolic time intervals in expressing global systolic and diastolic ventricular function. Left ventricular (LV) function has been shown to be abnormal in CAE with raised myocardial performance index (MPI), suggesting dyssynchronous contraction. MPI has been reported to be abnormally high in segments subtended by the ectatic coronary arteries (41). The relevance of these findings in the absence of other evidence supporting ischemia remains to be determined.

Therapeutic strategies

With the widespread availability of coronary angiographic investigations it is expected that more patients with CAE are likely to be identified with Major Acute Cardiac Events (MACE) (5). As such, the management of patients using an evidence-based approach needs to be established. The available treatment options include anticoagulants, anti-platelets, coronary vasodilators, angioplasty and CABG in certain cases, but medical management is widely accepted as the treatment of choice for non-obstructive CAE.

Oral anticoagulation vs. antiplatelet agents

In patients with pure CAE, treatment aim is to minimizing thrombosis risk from high inflammatory status and slow flow, and then oral anticoagulation may be an appropriate strategy (4). However, increased platelet activity and MPV remain a limitation when considering only oral anticoagulants. In patients with mixed CAE, Demplouse et al. (3) refuted the need for additional oral anticoagulation. This conflicting opinion on anticoagulation should not hamper the use of aspirin (42) in the presence of underlying atheroma. Dual antiplatelet therapy (DAPT) should

also be instituted if PCI is performed. Observations from Erden et al. (39) and others pointed out that the combination of triple anticoagulant therapy especially in acute setting of CAE with thrombus burden-related MI. While oral anticoagulant still to be considered even in non-ectasia related infarction as there is a potential to further thrombus formation in ectatic segments, as high as 32% (43).

However, glycoprotein inhibitors infusion as a routine treatment post PPCI seems a reasonable treatment strategy, yet its implication on the clinical outcome and prognosis is to be investigated.

Vasodilators

Coronary artery spasm is considered a main reason for ischemic symptoms in CAE with atherosclerosis. While nitrates are widely accepted as coronary vasodilators, for symptomatic relief of obstructive CAD, they may exacerbate stress-induced ischemia in isolated CAE (44), therefore not recommended. Instead, calcium channel blockers and β blockers might be considered as the main stay of vasodilator therapy for patients with CAE.

Surgical vs. percutaneous coronary intervention (PCI)

CAE related MI is generally managed as a primary PCI (PPCI), regardless the thrombus burden and reflow outcome. However, the presence of large thrombus burden within sizable CAE aneurysms has led to the introduction of a variety of operative procedures, including proximal and distal ligation, and even aneurysm resection. These interventions have also yielded good results (45, 46).

Coronary Artery Bypass graft (CABG), aneurysmectomy and only thrombectomy had been considered for many years in CAE with CAD, while the main indication for surgery is largely determined by the guidelines for the CABG surgery and patients suitability. PCI is a valuable option in CAE patients, with excellent early and late results in lesions adjacent to CAE segment as reported by Ochiai et al. (47) adequate stent expansion and wall apposition usually requires careful planning, which might be accomplished with IVUS. Stent deployment is currently considered the treatment of choice in symptomatic CAE patients with obstructive CAD. However, rationalizing stent deployment as a treatment for large CAE segment, with high predisposition to clot formation remains a clinical dilemma. Mechanical thrombectomy, on the other hand, may have a role in selected PPCI patients with large caliber vessels and heavy thrombus burden (48). While, thrombectomy devices vary from mechanical atherectomy devices for large caliber devices to aspiration atherectomy in acute fresh thrombus, yet no special devices have been produced to meet with adequate the need for atherectomy in CAE.

CAE prognosis

In general, CAE carries good prognosis, but high thrombus burden and poor reflow after intervention indicate a poor outcome, despite carrying good long-term survival (40). The out-

come of pure CAE seems to be better than that of obstructive CAD (43). Furthermore, recurrent pre-infarction (PA) angina in CAE known as the preconditioning effect of the myocardium contributes to good prognosis and outcome. PCI, in general, improves long-term prognosis of atherosclerotic CAE compared to conventional thrombolysis (33, 35).

Conclusion

The, previously described firm link between CAE and atherosclerotic CAD might limit lateral consideration of other underlying pathophysiology for CAE, particularly the pure form, and its effect on the myocardium and ventricular function. CAE may have serious effects from the high thrombosis burden leading to major acute cardiac events with related challenges, however, long term prognosis is satisfactory. Treatment strategies are not rationalized being based on small number of individual reports with conflicting opinion on oral anticoagulation, conservative and/ or interventional options. In acute STEMI presentation, the presence of ectasia may complicate PPCI procedures with poor reflow, but in general the presence of CAE should not change the standard management of MI according to the current guidelines. Future guidelines and development of the existing short-term management of CAE with STEMI, due to high thrombus burden, still to be rationalized.

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