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Coronary artery ectasia

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ABSTRACT

Coronary artery ectasia (CAE) is defined as localized or diffuse dilation of coronary artery lumen exceeding the largest diameter of an adjacent normal vessel more than 1.5 fold. The incidence of CAE is reported as 0.3–4.9% of patients undergoing coronary angiography. The rate of recognition may increase with the use of new non-invasive imaging methods as computed tomography (CT) and magnetic resonance (MR) coronary angiography. Atherosclerosis is considered as the main etiologic factor responsible for more than 50% of cases in adults while Kawasaki disease is the most common cause in children or young adults. Coronary ectasia is thought to be a result of exaggerated expansive remodeling, which is eventuated as a result of enzymatic degradation of the extracellular matrix and thinning of the vessel media. Patients with CAE without significant coronary narrowing may present with angina pectoris, positive stress tests or acute coronary syndromes. Ectatic vessel may be an origin of thrombus formation with distal embolization, vasospasm or vessel rupture. The prognosis of CAE depends directly on the severity of the concomitant coronary artery disease. Antiplatelet drugs underlie the therapy. Other management strategies in CAE involve both the prevention of thromboembolic complications and percutaneous or surgical revascularization.

Klíčová slova:
Aneurysma
Ateroskleróza
Ektázie
Koronární tepna

SOUHRN

Koronární ektázie (coronary artery ectasia – CAE) je definována jako lokalizované nebo difuzní rozšíření lumen koronární tepny o více než 1,5násobek průměru největší přilehlé nepostižené tepny. U pacientů absolvujících koronarografické vyšetření se incidence CAE uvádí v rozmezí 0,3–4,9 %. Vyhledávání osob s tímto postižením se může zvýšit při použití nových neinvazivních zobrazovacích metod, např. výpočetní tomografie (computed tomography – CT) a MR angiografie. Za hlavní etiologický faktor odpovědný za více než 50 % případů u dospělých je považována ateroskleróza, zatímco u dětí a mladých dospělých je nejčastější příčinou Kawasakiho nemoc. Předpokládá se, že koronární ektázie vzniká na podkladě nadměrné expanzivní remodelace v důsledku enzymatické degradace extracelulární matrix a ztenčování medie tepen. U pacientů s CAE bez významného zúžení koronárních tepen lze při vyšetření zjistit anginu pectoris, pozitivní výsledek zátěžového testu nebo akutní koronární syndromy. Při ektázii může v tepnách docházet k tvorbě trombů s následnou distální embolizací, vasospasmy nebo jejich rupturou. Prognóza CAE přímo závisí na závažnosti již přítomné ischemické choroby srdeční. Základem léčby jsou protidestičkové léky; mezi další formy léčby CAE patří prevence tromboembolických komplikací a perkutánní nebo chirurgická revaskularizace.

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Introduction

Coronary artery ectasia (CAE) is a well-recognized but relatively uncommon finding encountered during diagnostic coronary angiography [1–3]. It is commonly defined as inappropriate dilation of the coronary arteries exceeding the largest diameter of an adjacent normal vessel more than 1.5 fold [1,4] (Fig. 1). The term 'ectasia' refers to diffuse dilation of a coronary artery whilst focal dilation is called 'coronary aneurysm' [5]. Even though several mechanisms are suggested the pathophysiology of CAE is still underrecognized. Similarly no consensus exists about the natural history and management of this condition because of the relative scarcity of data. CAE represents not only an anatomical variant but also a clinical constellation of coronary artery disease (CAD) as association with myocardial ischemia and acute coronary syndromes. The purpose of this review is to update and summarize the clinical features of CAE.

Epidemiology and classification

Incidence of CAE detected by means of coronary arteriogram has been found to vary between 0.3% and 4.9% [1,3]. In the largest series from the CASS registry, Swaye et al. found CAE in 4.9% of coronary angiograms and the incidence is higher in men than in women (2.2% vs 0.5% respectively) [3] and postmortem incidence is given 1.4%. Advent of new non-invasive technologies such as computed tomography (CT) and magnetic resonance (MR) coronary angiography, may increase the rate of recognition [6]. Zeina et al. found the prevalence of CAE 8% by coronary CT angiography [7]. Markis suggested a classification of CAE according to the number and diffuseness of involved coronary vessels (Table 1) [7,8]. According to the diameter of the vessel lumen CAE is classified as small (< 5 mm), medium (5–8 mm) or giant (> 8 mm).

Etiology and pathophysiology

Atherosclerosis is considered as the main etiologic factor responsible for more than 50% of cases in adults [1,3,4,7,9] while Kawasaki disease is the most common cause in children or young adults [6–8]. Etiology of CAE is demonstrated in Table 2 [10,11]. There are marked histopathological similarities between ectasia and atherosclerosis. Arterial lumen may be narrowed, preserved or dilated with progression of atherosclerosis. The exact mechanism of luminal dilation in some atherosclerotic vessels is unclear while atherosclerosis predominantly causes narrowing of the vessel lumen. Certain plaques, as a result of a phenomenon so called 'arterial remodeling', do not reduce luminal size, presumably because of expansion of the media and external elastic membrane [12]. This finding also may be operative in the case of ectasia or aneurysm of other vessels. Observations with the use of intravascular ultrasound demonstrated that arterial remodeling may be bidirectional according to the expansion or shrinkage of external elastic membrane (i.e. positive and negative remodeling respectively) [12]. Positive (or expansive) remodeling is principally a compensatory mechanism to preserve luminal size during the progression of atherosclerosis. CAE is thought to be a result of exaggerated expansive remodeling in which both external elastic membrane and luminal size increase [11,13]. Enzymatic degradation of the extracellular matrix by matrix-metalloproteinases and other lytic enzymes and

Table 1 – Markis classification of coronary artery ectasia.

Types of CAE	Definition
Type 1	Diffuse ectasia of two or three vessels
Type 2	Diffuse ectasia in one vessel and localized disease in another
Type 3	Diffuse ectasia in one vessel only
Type 4	Localised or segmental involvement

Table 2 – Etiology of coronary artery ectasia.

- Atherosclerosis
- Coronary artery revascularisation procedures (balloon angioplasty, stent implantation, laser angioplasty, atherectomy, brachytherapy)
- Vasculitides (Kawasaki disease, polyarteritis nodosa, syphilis, Takayasu disease, Wegener granulomatosis, giant cell arteritis, Churg-Strauss syndrome)
- Congenital malformations
- Chest traumas
- Connective tissue disorders (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, ankylosing spondylitis, Behçet's disease, psoriasis)
- Collagenopathies (Marfan's syndrome, Ehlers-Danlos syndrome, hereditary hemorrhagic telangiectasia)
- Primary hyperaldosteronism

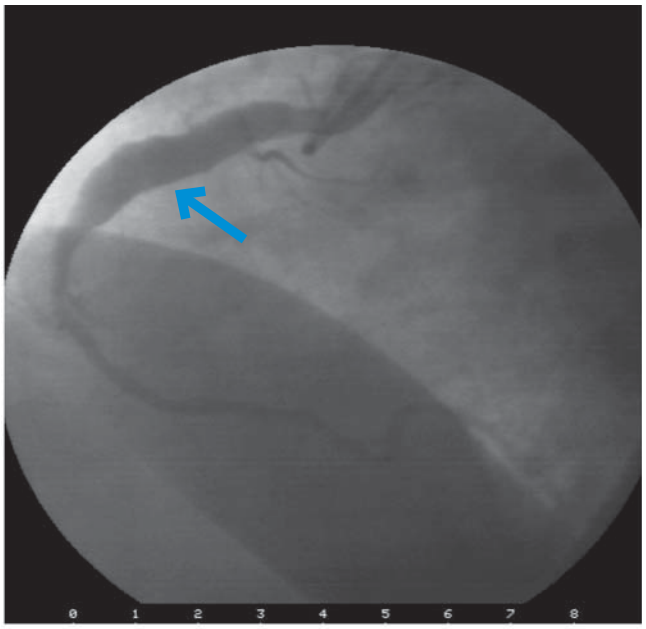

Fig. 1 – Ectasia of right coronary artery (arrow) in a 78 yo female patient.

thinning of the tunica media associated with severe chronic inflammation is suggested as the key pathogenetic mechanism of the exaggerated expansive remodeling. The severity of the changes in the media correlates positively with the diameter of ectasia. No evidence of ectasia is observed in cases with intact and uninvolved media layer [11]. CAE is associated with overexpression of matrix metalloproteinases [14]. Significantly higher levels of C-reactive protein (CRP) [15] and vascular endothelial growth factor (VEGF) [16] were found among patients with CAE, which suggests more severe and extensive inflammation and neovascularization in ectasia.

Association between the chronic stimulation of endogenous nitric oxide that leads to vascular relaxation and the occurrence of areas of ectasia is another suggested mechanism [2]. According to Manginas, CAE occurs due to two different mechanisms in two distinct patient groups: (i) rarely in subjects without coronary atherosclerosis as a result of interstitial NO vascular overstimulation and (ii) commonly in patients with concomitant CAD due to severe and chronic arterial inflammation [10].

Genetic predisposition of coronary ectasia could be suggested from its association with angiotensin-converting enzyme DD genotype [17] and with hereditary conditions as familial hypercholesterolemia [18].

There is controversial association between hypertension and CAE [3,7,8]. According to Zeina et al. CAE is not correlated with diabetes mellitus, hypertension, hyperlipidemia, smoking and family history of CAD [7]. CAE is also related to apical hypertrophic cardiomyopathy with high wall tension especially during ventricular systole [19]. Left ventricular diastolic dysfunction was demonstrated in CAE by conventional and tissue Doppler imaging in a small study [20].

Formation of aneurysm may be seen following percutaneous coronary interventions [9]. These may occur during coronary balloon angioplasty, but more importantly following coronary stent placement, atherectomy and brachytherapy [10,21]. Injury of the media of a blood vessel has still the main responsibility after percutaneous revascularization procedure for coronary aneurysm development [9]. Cardiac involvement is the most important manifestation of Kawasaki disease and includes coronary artery aneurysms and ectasias, premature atherosclerosis, thrombosis, or occlusion with myocardial infarction [22]. Coronary aneurysms develop in 15–25% of untreated children with Kawasaki disease [22,23], but after the introduction of the aspirin and intravenous gamma globulin therapy, resolution occurs in at least 50% of the cases [23]. Right coronary artery is the most frequently involved vessel in the coronary tree (40–61%) (Fig. 1) which is followed by the left anterior descending artery (15–32%) and left circumflex artery (15–23%) [1,3,6,7]. Isolated left main trunk ectasia is almost an exception. Ectasia is limited in one coronary artery in 75% of cases. CAE is mostly associated with obstructive coronary artery disease and isolated CAE has remarkably low incidence (< 20%). CAE may coexist with aneurysms of other arterial beds, particularly abdominal aorta, even with venous varicosities. This finding is conversely not supported by Hartnell et al. [1].

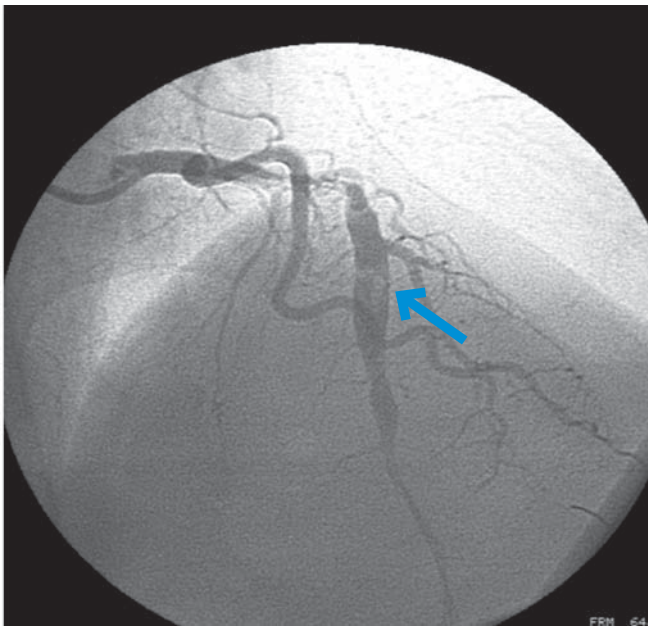

Fig. 2 – Ectasia of LAD mid segment and intracoronary thrombi (arrow) in a 65 yo male patient presented with acute coronary syndrome.

Diagnosis

Gold standard in diagnosing coronary ectasia is coronary angiogram. IVUS is available for evaluation of luminal extension and vessel wall pathologies and also for identification of normal arterial segments adjacent to stenotic lesions, which are often falsely characterized as aneurysms by conventional angiography [11]. Distortions in flow and washout are common in CAE, and are clearly associated with the severity of ectasia. Angiographic signs of turbulent and stagnant flow include delayed antegrade contrast filling, a segmental back flow (milking phenomenon) and local deposition of contrast in the dilated coronary segment (stasis) [5]. Other imaging methods as magnetic resonance angiography (MRA), multi-slice CT or the electron beam CT are also applicable for this vascular pathology [6]. However, CT should not be a choice as a technique for the follow up of patients because of its high radiation dose. Instead, MRA, being a non-invasive, non-radiating technique, may be utilized for follow up of CAE [5]. Transthoracic or transesophageal echocardiography may be option for the proximally located ectasias.

Clinical significance and symptoms

Clinical significance of CAE is not fully clarified. There is no typical symptom that could be associated with coronary ectasia. The symptoms may be associated with the concomitant CAD, Kawasaki disease or connective tissue disorder, although most of the patients are asymptomatic. Patients with CAE without significant coronary narrowing may still present with angina pectoris, positive stress tests, or acute coronary syndromes [24–26]. Decreased coronary flow velocity or stagnancy of coronary blood flow may cause exercise-induced angina regardless of coexisting stenotic coronary disease [5]. Additionally acute coronary

syndromes may result from atherosclerotic lesions within ectatic regions of the coronary arteries which appear to be highly inflamed high-risk plaques with tendency to rupture. Formation of intracoronary thrombus and dissipation of microemboli to distal coronary tree may also be the subject of acute coronary syndrome, which is precipitated from sluggish flow in the ectatic coronary segments [7,27] (Fig. 2). Angiographic findings such as topographical extent of CAE and corrected TIMI frame count are associated with severity of angina in patients with CAE [25]. Gulec et al. observed that in patients with isolated CAE, both epicardial flow and microvascular perfusion are diminished. Coronary microvascular perfusion is impaired even in the setting of normal epicardial flow [28]. CAE without significant epicardial stenosis may lead to exercise-induced myocardial ischemia especially if coronary tree is diffusely involved [24]. Akyurek et al. measured the blood flow velocity and coronary flow reserve invasively by use of Doppler scanning flow wire in patients with isolated CAE and in a control group. They reported significantly higher volumetric coronary blood flow but reduced coronary flow reserve in patients with diffuse CAE, suggesting that microcirculatory dysfunction may be the underlying cause of exercise-induced myocardial ischemia in CAE [29]. Ectatic coronary arteries tend to develop vasospasms which may also bring angina or acute coronary syndrome [7,30].

Observation of isolated CAE among patients younger than 50 must be suggestive of connective tissue disorders or vasculitides. In such circumstances further investigations must be under consideration. Moreover an overlooked diagnosis, Kawasaki disease must be realized in young adults presented with coronary aneurysm. The most important clinical features suggesting coronary aneurysms are due to Kawasaki disease are the history of Kawasaki disease compatible illness, Asian race, proximal location of coronary aneurysms, giant (> 8 mm) aneurysms, young age (< 30) and absence of significant coronary stenosis (≥ 50%). Accurate diagnosis of Kawasaki disease is important because the management strategies differ from conventional atherosclerotic ectasias [31].

Prognosis

The prognosis of CAE depends directly on the severity of the concomitant coronary artery disease. CAE with obstructive coronary artery disease is a vicious condition because of its potential of resulting in several adverse cardiac events. Although no difference in mortality between patients with or without CAE was demonstrated, isolated ectasia still bears risk of myocardial ischemia and infarction [5,24,28,29]. According to the classification defined by Markis, type I and type II coronary ectasias bring about the worse prognosis than type III and IV. Mortality rate at 2 years is reported 15% [8]. No relation between diameter of ectasia and survival is reported.

Treatment

There is still no consensus for management of CAE. Conducting large scaled randomized trials which compares different treatment modalities is difficult because of relative rarity of this condition. In the case of accompanying CAD, the management is the same as for CAD alone. Intense risk factor modification for primary and secondary prevention must be considered.

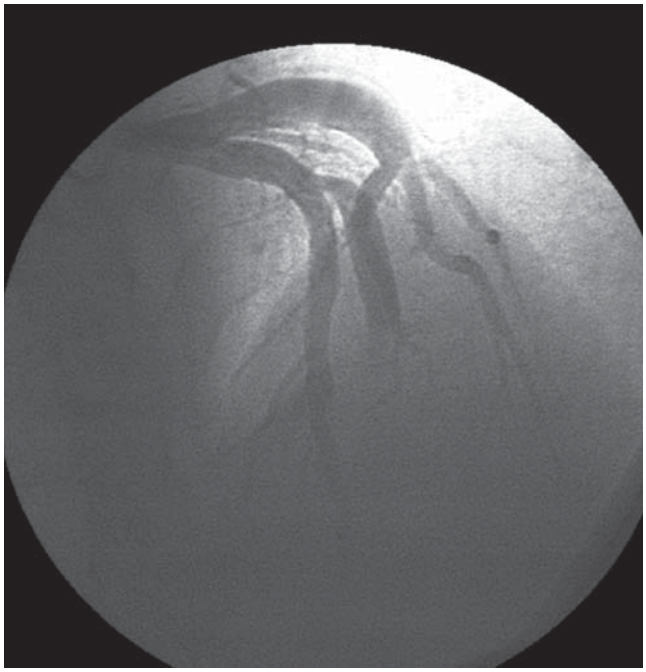

Fig. 3 – A 56 yo male patient presented with acute anterior MI. Diffuse ectasia and acute thrombotic occlusion was seen in LAD and huge diagonal artery.

Administration of aspirin to all CAE patients is logical due to the high coincidence with coronary artery disease and reported cases of myocardial infarction [5]. Statins may have a role by inhibiting matrix metalloproteinases [32]. Nitrates by dilating epicardial coronary arteries, may cause the steal syndrome and exacerbate anginal symptoms so they are not recommended [9,26]. Isolated CAE has a better prognosis and the antiplatelet drugs underlie the therapy [5]. Management of isolated coronary artery ectasia in the cases with angina or myocardial ischemia includes acetylsalicylic acid, statin and antiischemic medications (calcium channel blocker, beta-blocker and trimetazidine) as required [26,33,34] in addition to risk factor modification for atherosclerosis.

Acute coronary syndrome associated with CAE must be managed on an individual basis. Existence of thrombus may require to implement additional therapeutic decisions, i.e. thrombolysis, heparin infusion or glycoprotein IIb/IIIa receptor inhibitors as needed in the case of acute coronary syndrome [5,35–37] (Fig. 3). Thrombus aspiration during primary PCI should be considered [35]. Chronic anticoagulation is suggested by many authors, however, no randomized trial demonstrated its benefit on CAE. The anticipated benefit must be counterbalanced with the risk of hemorrhage. Percutaneous or surgical revasvularization may be option among patients with coexisting obstructive lesions and significant ischemia despite medical therapy [5,38,39]. Coronary intervention of stenosis adjacent to ectasia has inherent difficulties with

regards to optimal stent sizing, misplacement and embolization of the stent, early stent thrombosis and restenosis [5,40]. Extra care must be taken during stenting because adequate stent expansion and wall apposition is needed [10]. The implantation of covered stents offers superior results compared to the bare metal stents, but long term benefit has not been adequately proven [40]. Coronary aneurysm formation after drug-eluting stent implantation is also notified as a rare complication [41,42]. Parallel stenting with two drug-eluting stents has been reported in an ectatic coronary artery stenting [43]. The use of large sized peripheral stents in ectatic coronary arteries also may be possible [44]. Indications for surgical treatment are identical to those in the case of coronary heart disease [9]. Additionally in those patients with evidence of enlargement of saccular coronary artery aneurysms with increased risk of rupture surgical resection may be an alternative [45,46]. As previously mentioned the usage of aspirin and intravenous gamma globulin therapy reduces the occurence of coronary ectasias in patients with Kawasaki disease [23].

Conclusion

CAE is a vascular disease mostly a form of atherosclerosis seen in 0.3–4.9% of diagnostic coronary angiography procedures. A pattern of vascular remodeling, exaggerated expansive remodeling with enzymatic degradation of the extracellular matrix and thinning of the vessel media as a result of chronic inflammation is thought to be a major pathophysiologic process. The symptoms may be associated with the concomitant CAD, Kawasaki disease or connective tissue disorder although most of the patients are asymptomatic. Clinical importance especially leans on its association with acute coronary events. Treatment options include: risk factor modifications for CAD, antiischemic therapy, antithrombotic management and percutaneous or surgical revascularization techniques. Future trials are warranted in order to optimize the management of CAE.

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