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Review

Pathogenetic mechanisms of coronary ectasia

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Abstract

Coronary ectasia is defined as local or generalized aneurysmal dilatation of the coronary arteries. The present review summarizes the molecular, cellular and vascular mechanisms which are involved in the pathobiology of coronary ectasia. Coronary ectasia likely represents an exaggerated form of expansive vascular remodeling (i.e. excessive expansive remodeling) in response to atherosclerotic plaque growth. Enzymatic degradation of the extracellular matrix of the media is the major pathophysiologic process that leads to ectasia. Atherosclerotic lesions within ectatic regions of the coronary arteries appear to be highly inflamed high-risk plaques with proclivity to rupture. Better understanding of the pathogenetic processes involved in coronary ectasia is anticipated that will provide a further insight into the clinical significance and natural history of this entity, and may also have direct clinical implications in the management and follow-up strategy of this condition.

Keywords: Ectasia; Coronary atherosclerosis; Vascular remodeling; Molecular biology

1. Introduction

Aneurysms in the human coronary arteries are a controversial phenomenon and the subject of an ongoing debate since many issues on them remain obscure. In contrast to discrete aneurysms recognized in certain cases, the terms aneurysmal coronary artery disease, dilating arteriosclerosis or coronary artery ectasia are commonly used to denote a more generalized defect affecting the coronary tree, often in the presence of atherosclerosis [1,2]. Instead of representing a simple anatomic variation, ectasia has direct clinical implications, as it has been linked to clinical manifestations of coronary artery disease (CAD), such as stable angina and acute coronary syndromes [3–5]. Everyday clinical practice tends to underestimate the impact of coronary ectasia merely due to the yet unknown natural history of this condition, its relative rarity and the subsequent difficulties in conducting randomized trials to compare different forms of treatment. The continuously expanding implementation of coronary angiography in the investigation of cardiovascular disease is likely to culminate in higher absolute numbers of patients diagnosed with coronary ectasia. In this setting, the need for appropriate clinical recommendations should not be overlooked.

The purpose of this review is to summarize the molecular, cellular and vascular mechanisms, which are involved in the pathobiology of aneurysmatic lesions within the coronary arteries. Understanding these mechanisms may be of particular importance on acquiring an insight into the nature of coronary ectasia and its possible relation to the atherosclerotic process, and may also have direct clinical implications in the management and follow-up strategy of this condition.

2. Definition and classification

Coronary ectasia is arbitrarily defined as localized or diffuse dilatation of the coronary lumen exceeding the diameter of normal adjacent segments or the diameter of the patient's largest coronary artery by 1.5 times [6]. On the basis of their luminal

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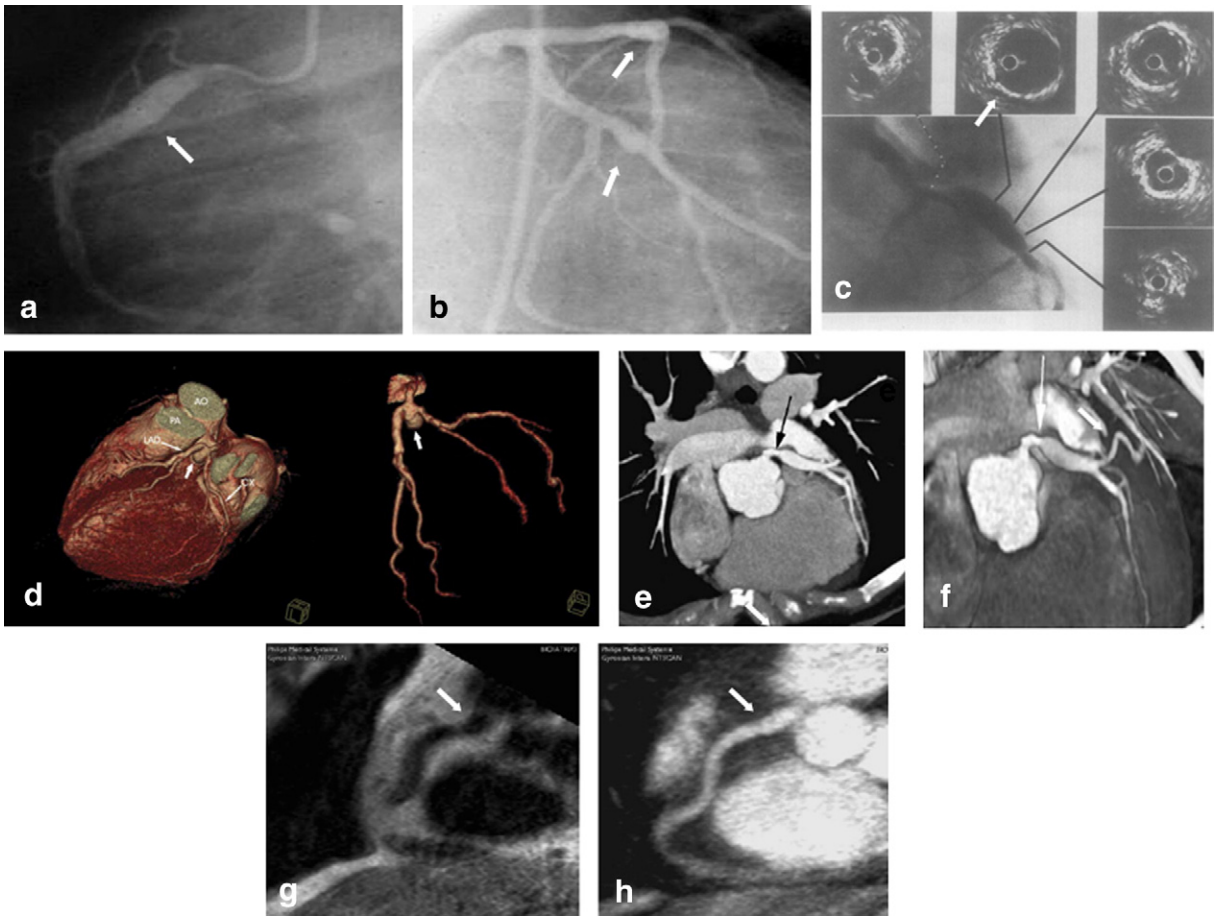

Fig. 1. a. Diffuse ectasia (type III) of the right coronary artery (arrow), b. Segmental ectatic lesions (type IV) of the left coronary artery (arrows), c. IVUS depiction of a fusiform coronary aneurysm (arrow) between atherosclerotic segments (reprinted from [14]) d, e, f. CT images of left coronary artery aneurysms (arrows; reprinted from [17] and [18]), g, h. Coronary magnetic resonance angiograms employing black-blood (left) or white-blood (right) contrast from a patient with ectatic right coronary artery (arrows; reprinted from [19]).

diameter, coronary aneurysms are classified as small (<5 mm), medium (5–8 mm) or giant (>8 mm) [7]. A further geometric classification defines an aneurysm as saccular when its maximum transverse diameter exceeds its longitudinal aspect, and as fusiform when its longitudinal dimension is greater than its maximum transverse diameter [8]. Also, coronary aneurysms are classified as true, when the vascular wall contains all normal vascular layers, or as pseudoaneurysms (typically saccular), when there is a loss of normal vascular wall integrity, resulting in the formation of thin-walled structures that lack normal arterial wall layers [8]. As for its topographical extent in the major epicardial coronary arteries, ectasia is subcategorized in the following 4 types: type I, diffuse ectasia of two or three arteries; type II, diffuse disease in one artery and localized in another;

Table 1
Classification of coronary aneurysms

Characteristic	Categories	Description
Luminal diameter	Small	Luminal diameter of the aneurysm <5 mm
	Medium	Luminal diameter of the aneurysm 5–8 mm
	Giant	Luminal diameter of the aneurysm >8 mm
Transverse and longitudinal size	Saccular	The maximum transverse diameter exceeds the longitudinal dimension of the aneurysm
	Fusiform	The longitudinal dimension exceeds the maximum transverse diameter of the aneurysm
Vascular wall integrity	True aneurysms	All normal vascular layers present
	Pseudo aneurysms	Loss of normal vascular wall integrity
Topographical extent	Type I	Diffuse ectasia of two or three vessels
	Type II	Diffuse ectasia in one vessel and localized in another
	Type III	Diffuse ectasia of one vessel only
	Type IV	Localized or segmental ectasia

Table 2
Prevalence of coronary ectasia in angiographic series

Source	Number of subjects	Prevalence (%)
Swaye et al. [1]	20,087	4.9
Giannoglou et al. [9]	10,524	2.7
Tunick et al. [10]	8,422	0.2
Hartnell et al. [10]	4,993	1.4
Markis et al. [6]	2,457	1.2

type III, diffuse ectasia of one artery only (Fig. 1a); type IV, localized or segmental ectatic lesions [6] (Fig. 1b) (Table 1).

3. Epidemiology

The prevalence of aneurysmal coronary disease in angiographic series varies between 0.2 and 10% (Table 2) [1,6,9–11]. Coronary Artery Surgery Study registry studied 20,087 subjects and reported a prevalence rate of 4.9% [1]. Recently, we reported a prevalence rate of 2.7% in an angiographic series of 10,524 patients [9]. A prevalence of 1.4% for coronary aneurysms was reported in an autopsy study of 694 consecutive subjects, which still lies within the range of the other angiographic series [12]. However, the above frequencies may not be representative of the actual prevalence of coronary aneurysms in the general population, as there is a selection bias in patients referred for diagnostic coronary angiography. Furthermore, different demographic characteristics of the populations studied, as well as genetic heterogeneity of the subjects may account for the differences in the frequency of ectasia in the above reports. Also, as the angiographic diagnosis of ectasia is operator dependent, inter-observer variability may merely be responsible for the prevalence discrepancies in different cohorts.

4. Etiology

The co-existence of coronary ectasia with coronary atherosclerosis raised the concept that ectasia may represent a variant of CAD [1,2,6,9]; however a definite link between atherosclerosis and ectasia has not been confirmed. Furthermore, coronary aneurysms are seen in association with systemic inflammatory vasculitides (e.g. polyarteritis nodosa, Kawasaki disease, Takayasu arteritis, Behçet's disease), connective tissue disorders (e.g. rheumatoid arthritis, systemic lupus erythematosus, scleroderma, ankylosing spondylitis), hereditary collagen defects (e.g. Ehlers–Danlos syndrome, Marfan syndrome, hereditary hemorrhagic telangiectasia), bacterial infections and congenital malformations [13]. Moreover, aneurysmatic lesions (mostly pseudoaneurysms) may occur after coronary interventions, such as balloon angioplasty, stent implantation, directional coronary atherectomy, pulsed laser coronary angioplasty and brachytherapy [13].

5. Diagnosis

Coronary angiography is the gold standard in the diagnosis of coronary aneurysms, providing information not only for their shape, size, topography and extent, but also for the presence of coexistent coronary stenoses (Fig. 1a and b). Intravascular ultrasound provides a more detailed visualization of the arterial wall and can identify normal arterial segments adjacent to stenotic lesions, which are often falsely characterized as aneurysms by conventional angiography [14,15] (Fig. 1c). Moreover, intravascular ultrasound can distinguish a true aneurysm from a pseudoaneurysm [16]. Non-invasive diagnostic modalities such as transthoracic echocardiography [13], computed tomography [17,18], and magnetic resonance imaging [19] are also useful in the diagnosis of coronary ectasia (Fig. 1d–h).

6. Natural history and clinical manifestation

The clinical presentation of coronary aneurysms varies from asymptomatic to atypical chest pain, stable angina and acute coronary syndromes. In cases where coronary aneurysms accompany coronary stenoses, the symptoms are most commonly associated with the extent and severity of coexisting obstructions [1,6]. However, isolated coronary ectasia without being associated with coronary stenosis may also present with stable angina [20], positive treadmill test [4], increased levels of biochemical markers [3] or even myocardial infarction [5]. The natural history and clinical manifestation of coronary ectasia was investigated in a series of 3,870 subjects undergoing coronary angiography. In the subgroup of patients presenting with an acute coronary syndrome, coronary ectasia was associated with the culprit lesion in one third of cases [21]. Another study prospectively assessed the clinical outcome of 54 patients with an angiographic diagnosis of ectasia. A major cardiac event on follow-up was documented in 37% of cases [22]. Finally, in a small follow-up study of five patients with ectasia who suffered a myocardial infarction, the clinical event was attributed to thrombus formation in a previously non-stenosed aneurysmatic arterial region [5].

Further insight into the natural history of ectasia comes from experimental animal data, which demonstrated that high-risk plaques with severe lipid infiltration and inflammation and thin fibrous cap develop in coronary artery regions which exhibit localized dilatation (aneurysm) of the arterial wall (Fig. 3) [23]. These experimental findings in combination with the clinical outcome studies suggest that coronary ectasia is linked to plaque instability with an increased risk for future adverse cardiovascular outcome. However, not all the ectatic lesions exhibit follow similar natural history trajectory and the explanation of this remains to be further investigated.

7. Histopathology

There are several histopathologic similarities between ectasia and atherosclerosis. Aneurysmatic coronary segments demonstrate a marked degradation of the medial collagen and elastin fibers with disruption of the internal and external elastic lamina [2,6,12]. These findings, in association with the observation that cases in which the media was intact and uninvolved had no

evidence of ectasia, suggest that the enzymatic degradation of the media may be a key component in the pathogenesis of coronary ectasia [6]. Of note, the severity of the changes in the media correlates positively with the diameter of aneurysmal lesions [24]. Chronic inflammatory infiltration of monocytes and lymphocytes in the media and adventitia, as well as neovascularization and intramural hemorrhage within the media have also been decribed [25].

8. Pathophysiology of ectasia: role of enzymatic degradation of extracellular matrix

Based on the clinical presentation and histopathologic findings, it has been suggested that coronary ectasia represents a particular form of arterial remodeling in response to local plaque growth. Arterial remodeling refers to alterations in the total arterial cross sectional area i.e. the area within the external elastic membrane in response to local hemodynamic and biochemical factors [26]. Three distinct remodeling patterns have been described: (a) constrictive remodeling representing shrinkage of external elastic membrane and lumen area, (b) compensatory expansive remodeling, in which the total external elastic membrane area increases, but the lumen is preserved, and (c) excessive expansive remodeling, in which both external elastic membrane and lumen size increase [23,26–29].

Coronary ectasia could be considered as an exaggerated form of excessive expansive remodeling since enzymatic degradation of the extracellular matrix (ECM) of the media appears to be a fundamental pathobiologic process in both conditions [23,27–29]. Overexpression of matrix metalloproteinases (MMPs) has been associated with expansive arterial remodeling in experimental animal models [30], while their suppression acts against it [31]. In humans, abdominal aortic aneurysms have been associated with increased production of MMPs [32] while post-mortem studies also support the role of MMPs in expansively remodeled coronary arteries [33]. Increased expression of the MMP-3 gene was reported as an independent predictor of coronary aneurysms [34]. Other classes of proteolytic enzymes such as cystein proteinases (e.g. cathepsins K, L, and S) and serine proteinases (e.g. neutrophil elastase, plasminogen activators, plasmin, chymase and tryptase) may play an important role in the pathogenesis of coronary ectasia [35–38]. Matrix degrading enzymes may cause severe disruption of the internal elastic lamina providing a gateway for the inflammatory cells to extend from the intima into the media, elaborate matrix proteases, degrade the collagen and elastin fibers, weaken the arterial wall integrity, and ultimately promote an ectatic transformation of the wall [28,31,39].

9. Factors associated with coronary ectasia

A variety of factors may influence the formation of ectasia by inducing activation of matrix degrading enzymes and subsequent excessive expansive remodeling. The majority of these are either directly or indirectly linked to the atherosclerotic process (Fig. 2).

9.1. Role of lipoproteins

Indirect evidence for an association between plasma lipoprotein levels and coronary artery aneurysms comes from reports in cases of familial hypercholesterolemia [40,41]. One study found that coronary ectasia is more frequent in patients with heterozygous familial hypercholesterolemia than in healthy controls, and is associated with reduced high-density lipoprotein cholesterol (HDL-C) levels [42]. Interestingly, reduction of serum low-density lipoprotein cholesterol (LDL-C) levels by repeated plasma exchange in a patient with heterozygous familial hypercholesterolemia led to angiographic improvement of coronary ectasia [43]. At the molecular level, LDL-C binds elastin, collagen and proteoglycans [44], and undergoes oxidative modification which further increases its affinity to matrix components. Oxidized LDL-C is subsequently engulfed by macrophages and smooth muscle cells resulting in foam cell formation. Foam cells in turn enhance active breakdown of the extracellular matrix by elaborating matrix degrading enzymes [45]. Also, oxidized LDL-C upregulates MMPs [46].

9.2. Role of inflammation

9.2.1. Role of adhesion molecules

Inflammation plays a key role in the aneurysm formation in the coronaries, as well as in the systemic circulation. Adhesion molecules take part in the pathogenesis of atherosclerosis by mediating the adherence and transmigration of circulating monocytes across the vascular endothelium. Plasma levels of E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) were significantly higher in patients with isolated ectasia compared with patients with obstructive coronary artery disease alone, or with normal coronary arteries. A significant positive correlation between the levels of these adhesion molecules and the length of vascular segments with ectasia was also found [47]. Higher levels of ICAM-1 and VCAM-1 were also noted in cases with a combination of ectasia and obstructive coronary artery disease [48].

9.2.2. Role of C-reactive protein (CRP)

CRP levels have been found significantly higher in patients with isolated coronary ectasia, than in those with obstructive coronary disease or normal coronary arteries, suggesting a more severe and extensive inflammatory cell infiltration in patients with ectasia [49].

9.2.3. Role of vascular endothelial growth factor (VEGF)

VEGF has potent angiogenic properties and possesses an important role in inflammatory processes. Significantly higher

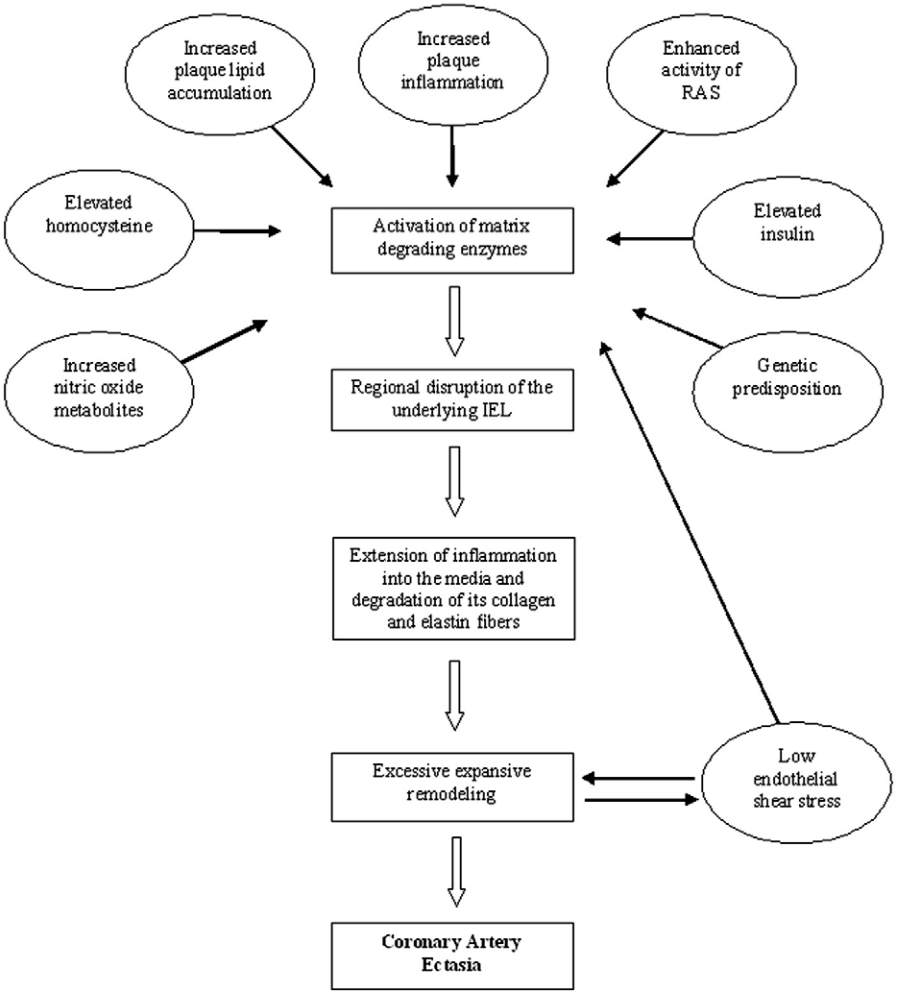

Fig. 2. Schematic overview of the pathogenesis of coronary artery ectasia. A variety of factors implicated in the atherosclerotic process promote the expression and activity of matrix degrading enzymes, which cause severe disruption in the internal elastic lamina (IEL) and provide a gateway for the inflammatory cells to extend into the media, favouring excessive expansive remodeling and ultimately leading to formation of coronary ectasia. RAS: renin–angiotensin system.

VEGF levels were found in patients with diffuse coronary ectasia [50]. This comes in consistence with neovascularization being described in aneurysmatic arterial regions, while it is also an established feature of atherosclerosis [25]. Furthermore, VEGF triggers the formation of MMPs, thus creating a vicious cycle which maintains and progresses structural alterations in the vascular wall [51].

9.2.4. Role of leukotriens

Leukotriens are abundantly expressed in atherosclerotic lesions, and are linked to higher atherosclerotic burden and CAD manifestations [52]. In experimental models, increased expression of the 5-lipoxygenase gene predisposed to aortic aneurysm formation [53]. 5-lipoxygenase overexpression co-localized with MMPs release by macrophages within the vascular wall [54].

9.2.5. Role of infectious agents

As for the contribution of infectious agents in the development of aneurysms in the coronary arteries, particular attention has been given to the role of *Chlamydia pneumoniae*, an agent that is implicated in the pathogenesis of atherosclerosis. Antibodies against *C. pneumoniae* were higher in patients with isolated coronary ectasia than in normal controls, independently of established risk factors for atherosclerosis [55]. The implication of *C. pneumoniae* in coronary ectasia is likely mediated by the production of heat-shock protein 60 which regulates the expression of MMPs [56,57].

9.3. Role of renin–angiotensin system

Angiotensin II is a major determinant of vascular wall homeostasis as it favors atherosclerosis via inducing endothelial dysfunction, expression of inflammatory mediators, generation of oxidative stress, cellular proliferation, fibrosis and thrombosis [58]. A specific genetic polymorphism leading to increased plasma and tissue levels of angiotensin II was associated with coronary ectasia [59]. Elevated angiotensin II levels may facilitate the degradation of the media by inducing interleukin-6 which in turn

stimulates the activity of matrix degrading enzymes providing a link to ectasia [60].

9.4. Role of homocysteine

In case control studies, plasma homocysteine levels were significantly higher in patients with isolated coronary ectasia, than in control subjects with angiographically normal coronary arteries [61,62]. Also, no significant differences in plasma homocysteine levels were found among patients with coronary ectasia and those with coronary artery disease [62]. Homocysteine levels were also positively correlated with the number of the coronary segments with ectasia, but not with the mean diameter of the ectatic lesions [61]. Elevated homocysteine levels may facilitate the degradation of the medial arterial layer by inducing serine proteinase activity in arterial smooth muscle cells, as well as by activating MMP-2 [63].

9.5. Role of insulin

Insulin is implicated in both atherosclerosis and coronary ectasia. As for its relation to coronary ectasia, a study revealed an association between fasting plasma insulin levels and coronary ectasia among patients with heterozygous familial hypercholesterolemia [64]. Hyperinsulinemia may exacerbate the remodeling process in the setting of coronary atherosclerosis, by stimulating the proliferation and migration of vascular smooth muscle cells from the arterial media and interfering with extracellular matrix production [65].

9.6. Role of nitric oxide (NO)

NO, which is well known for its vasodilatory, anti-inflammatory, anti-apoptotic and anti-thrombotic effects may generate metabolites, which predispose to ectasia. Indirect evidence for such an association came from a report of increased frequency of ectasia among individuals previously exposed to herbicide sprays. Herbicide sprays increase acetylocholine, which in turn stimulates NO production [66]. Expression of inducible NO synthase (iNOS) and plasma levels of NO end-products were also increased in an animal model of abdominal aortic aneurysm, while inhibition of iNOS limited aneurysm expansion [67]. Another study showed that iNOS upregulation was followed by increased MMPs expression [68], providing a plausible molecular link with aneurysm formation. Furthermore, NO by-products (e.g. peroxynitrate, nitrate) appear to play an important role in coronary ectasia by activating latent MMPs [69,70].

9.7. Role of coronary local hemodynamics

Local coronary flow environment may lead to coronary ectasia. Atherosclerotic lesions develop and progress in arterial regions with low endothelial shear stress [71]. Recent

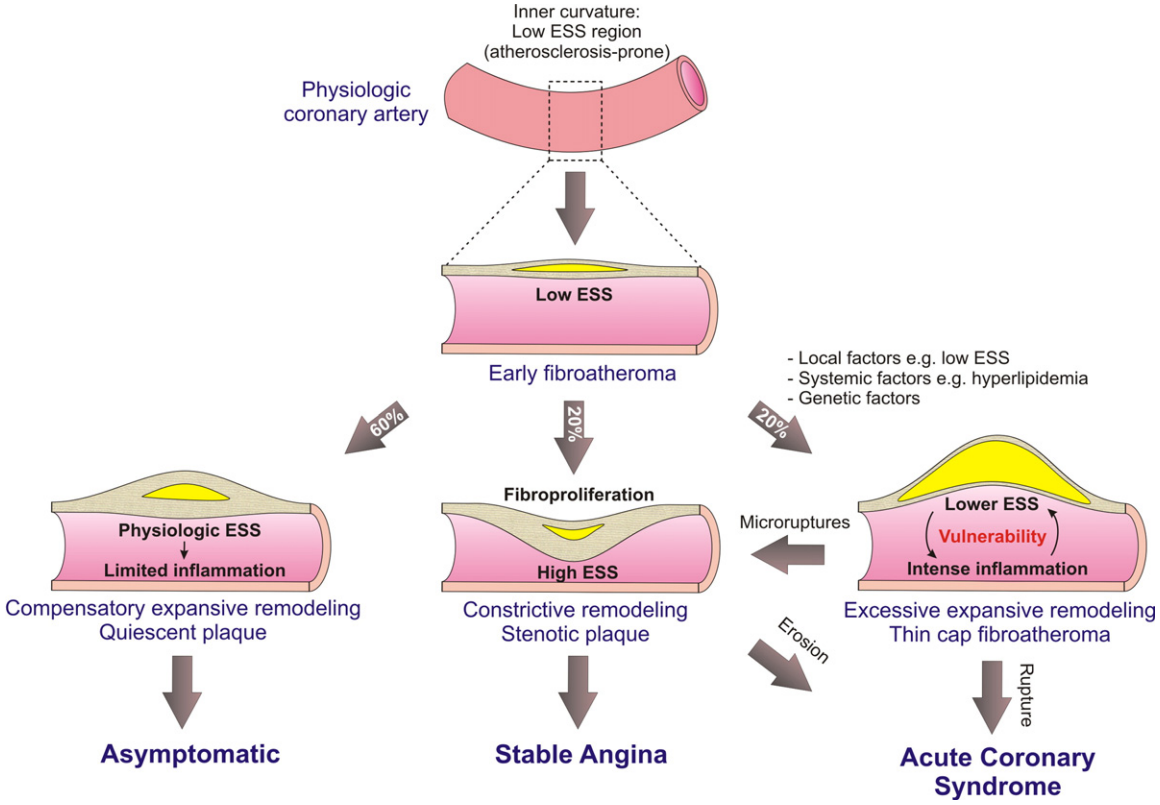

Fig. 3. Natural history of coronary atherosclerosis. Arterial regions with localized aneurysm (excessive expansive remodeling) create a vascular environment that promotes the transformation of an early atherosclerotic lesions to a thin cap fibroatheroma, which leads to an acute coronary syndrome (reprinted from [28]).

histopathology studies have also showed that high-risk atherosclerotic plaques with intense lipid accumulation, inflammation, internal elastic lamina degradation and excessive expansive remodeling develop in areas in which low endothelial shear stress occurs [23,28,29]. Within that vascular environment in a locally expanded coronary region, low endothelial shear stress is perpetuated, fostering the formation of ectasia and ultimately transformation of an atherosclerotic lesion into a high-risk plaque (Fig. 3) [23,28].

Hypertrophic cardiomyopathy may also predispose to the formation of coronary ecstatic lesions. The abnormally high wall tension of the hypertrophic myocardium may act as giant muscle bridge, causing systolic blood flow cessation. High intraluminal pressure and subsequently high tensile stress, especially during ventricular systole, may consequently promote the ectatic vascular transformation within the bridge [72,73].

9.8. Role of genetic predisposition

Some indirect evidence for the influence of genetics to the development of coronary ectasia comes from its association with the angiotensin converting enzyme genotype [59] and also with hereditary conditions like familial hypercholesterolemia [40,41]. Genetic variations may also account for the differences in the frequency of ectasia in certain geographical regions [11]. Of interest, African American race was found as a protective factor against the formation of coronary aneurysms in children with Kawasaki disease [74]. However, no definite genetic defect, which would lead to ectasia has yet been shown.

10. Ectasia: local or generalized condition?

Another feature of aneurysmal coronary disease, probably requiring special consideration is its frequent occurrence in association with more widespread vascular abnormalities. Several studies have demonstrated increased prevalence of coronary aneurysms in patients with aneurysms in the thoracic and abdominal aorta, the pulmonary, iliac, femoral, popliteal, anterior communicating and basilar artery [13]. Furthermore, varicosities of the coronary veins frequently coexist with coronary aneurysms [20], while varicose veins [75] and varicocele [76] have been recorded with higher frequencies among patients with coronary ectasia. These data suggest a more generalized vascular defect, affecting not only the arterial but the venous system as well. An example of a generalized disease associated with coronary ectasia is Kawasaki syndrome, an acute febrile childhood vasculitis of unknown origin that leads to coronary, as well as systemic, aneurysm formation. Increased levels of inflammatory mediators (e.g. VEGF) [77] and matrix degrading enzymes (e.g. MMPs, neutrophil elastase) have been reported in this condition [78]. Another pathway via which Kawasaki disease may trigger aneurysm formation involves induction of NO and its detrimental metabolite, peroxynitrite [79].

11. Conclusion

Ectasia is a coronary abnormality, which constitutes a localized or diffuse dilatation of the vascular wall and lumen. Activation of proteolytic enzymes and enzymatic degradation of the media are the most critical molecular events leading to a structural defect of the coronary wall, and eventually aneurysm formation. This is mediated via several factors involved in the atherosclerotic process, such as accumulation of lipoproteins into the intima, inflammatory cell infiltration, rennin–angiotensin system activation and generation of oxidative stress, which lead to excessive expansive arterial remodeling. Altered NO metabolism and coronary hemodynamics, in particular low endothelial shear stress, also play a role, whereas the effect of genetic background is yet under investigation.

Data presented in this review support the presence of common underlying molecular mechanisms involved in the development of ectasia, atherosclerosis and excessive expansive remodeling. Taking into consideration the complexity of these processes and numerous different interactions involved, it would be difficult to claim such an association for the entirety of cases with aneurysmal coronary dilatation. However, it would be useful for clinicians to be aware of the evidence that coronary ectasia develops in an intensively inflamed vascular wall, which predisposes to plaque instability and increased risk of adverse cardiovascular events despite preservation of the coronary lumen. Further experimental investigations are needed to reveal the molecular mechanisms involved in ectasia. In addition, large-scale clinical studies are warranted to shed light into the clinical manifestation and natural history of coronary ectasia.

Competing interests

None declared.

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