REVIEW

Change of paradigm in pathogenesis of non-ST segment elevation myocardial infarction (NSTEMI)

Rodica Dan[1], Lucian Petrescu[1]

Abstract: The pathogenesis of the acute coronary syndrome (ACS) is very complex and not fully clarified, bringing in front the questions regarding the differences between acute coronary syndrome with ST segment elevation (STEMI) and the one without ST segment elevation (UA/NSTEMI), because there isn't always a ruptured plaque beneath all coronary thrombi. Indeed, plaque rupture declines as a cause of ACS, while superficial erosion appears on the rise, and STEMI wanes as NSTEMI waxes. There is a change in the character of human plaques in the statin era: they are getting less fatty and less "inflamed". The plaques prone to erosion: have a poor lipid content, are rich in proteoglycan and glycosaminoglycan, with non-fibrillar collagen breakdown, few inflammatory cells, endothelial cells apoptosis and secondary neutrophil involvement, they appear more frequently in patients with diabetes, with high triglycerides and have a female predominance. Understanding the pathogenesis is essential regarding the potential effective treatment: in patients with plaque erosion, as inflammation represents an intense local thrombogenic stimulus, a potent antithrombotic treatment might be one of the treatment choice, so the treatment choice expands beyond the traditional focus on reducing stenoses.
Keywords: acute coronary syndrome, plaque erosion, plaque rupture, inflammation

Rezumat: Patogenia sindroamelor coronariene acute (SCA) e foarte complexă şi nu pe deplin înţeleasă, în ceea ce priveşte diferenţa dintre SCA cu supradenivelare de segment ST (STEMI) şi cel fără supradenivelare de segment ST (AI/NSTEMI), pentru că nu orice tromb coronarian acoperă o placă ruptă. Într-adevăr, se pare că placa ruptă se întâlneşte mai rar ca şi cauză a SCA, în timp ce eroziunea superficială a plăcii e tot mai frecvent descoperită şi descrisă, odată cu scăderea frecvenţei STEMI, respectiv creşterea numărului cazurilor de NSTEMI. Există apoi o modificare a caracteristicilor plăcilor aterosclerotice în era utilizării pe scară largă a statinelor: plăcile sunt mai puţin grase şi mai puţin inflamate. Aceste plăci cu risc de eroziune: au un conţinut lipidic redus, un conţinut bogat în proteoglicani şi glicozaminoglicani, cu fisuri ale colagenului non-fibrilar, puţine celule inflamatorii, apoptoza celulelor endoteliale şi implicare neutrofilică secundară, fiind mai frecvent întâlnite la femei, diabetici sau la pacienţii cu hipertrigliceridemie. Înţelegerea patogeniei e esenţială şi în abordarea terapeutică eficientă: cum la pacienţii cu plăci erodate, inflamaţia reprezintă un intens stimul trombogenic local, unul din tratamentele de ales ar fi cel antitrombotic, extinzându-se astfel opţiunile terapeutice, dincolo de reducerea stenozei.
Keywords: sindrom coronarian acut, placă erodată, placă ruptă, inflamaţie

INTRODUCTION

Atherosclerotic vascular disease continue to represent the leading cause of death in Western countries, but not only there, and among the different manifestations or forms of presentation, the acute coronary syndrome (ACS) plays an important role. Patients with ACS present with unstable angina (UA), acute myocardial infarction (AMI) and sudden coronary death (SCD). Most of the ACS are thought to be the result of sudden luminal thrombosis, which occurs from three different pathologies: plaque rupture, plaque erosion and calcified nodules.

Plaque rupture is defined as a lesion consisting of a necrotic core with an overlying thin ruptured fibrous cap that leads to luminal thrombosis because of contact of platelets with a highly thrombogenic necrotic core.

Plaque erosion shows a luminal thrombus with an underlying base rich in proteoglycans and smooth muscle cells with minimal inflammation. Most erosion lesions are devoid of a necrotic core, but when present, the core does not communicate with the lumen because of a thick fibrous cap.

The least common of all lesions is the calcified nodule, that shows an underlying calcified plate with superimposed bony nodules that result in discontinuity of the fibrous cap and is devoid of endothelial cells with overlying luminal thrombus[1].

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Complex pathogenesis of ACS

For 10 years now, we are talking about an essential term, considered a precursor lesion of ACS: vulnerable plaque, that, as we all know, should be reserved for plaques that resemble all three causes of luminal thrombosis: thin cap fibroatheroma (TCFA), pathologic intimal thickening and calcified plaque with luminal calcified nodules[1]. What did Renu Virmani and her colleagues observed and described? That the non-thrombosed lesion that most resembles the acute plaque rupture is the thin cap fibroatheroma (TCFA), which is characterized by a necrotic core with an overlying fibrous cap measuring <65µm, containing rare smooth muscle cells (SMC), but numerous macrophages. Thin cap fibroatheromas are most frequently observed in patients dying with acute myocardial infarction (AMI) and least common in plaque erosion. They are most frequently observed in proximal coronary arteries, followed by mid and distal major coronary arteries. Thin cap fibroatheromas are common in patients with high total cholesterol (TC) and high TC/high-density lipoprotein cholesterol ratio, in women >50 years and in those patients with high levels of high sensitivity C-reactive protein. The important idea driven from these observations was that identification of this type of lesions in living patients might help reduce the incidence of SCD.

So, we admit that the pathogenesis of the ACS is very complex and not fully clarified, bringing in front the questions regarding the differences between two major players: acute coronary syndrome with ST segment elevation (STEMI) and the one without ST segment elevation (UA/NSTEMI). We must not forget that a ruptured plaque is not found beneath all coronary thrombs.

As Giampaolo Niccoli, Francesco Fracassi and Filippo Crea mentioned in "*Pathophysiology and clinical significance of plaque rupture*"[2]: clinical instability is heterogeneous from many points of view – some patients have only one episode of ACS that will not repeat during their lifetime, others present multiple, recurrent, episodes; some cases present with severe stenoses, others, only with mild/moderate lesions; plaque severity (but not only from the percentage of stenose's point of view) leading to ACS is heterogeneous, when we are looking at the morphology and the composition of the plaque, as post-mortem studies and intravascular imaging have shown that ACS can be associated with: plaque rupture, plaque erosion or the presence of a smooth plaque[1,3,4].

But, how many plaques with morphologic characteristics associated with vulnerability do not cause a fatal rupture? This is one essential question brought up by Peter Libby and Gerard Pasterkamp in "*Requiem for the vulnerable plaque*", because more recent evidences suggest that plaques with thin fibrous caps and large lipid pools actually seldom rupture and cause clinical events. Multiple so called "active" plaques often reside in the coronary and other arteries. Intravascular imaging studies in humans using ultrasound or optical coherence tomography (OCT) have proved particularly illuminating: thin-capped plaques do not inevitably rupture and cause thrombotic events! Contemporary data do not support the "vulnerability" of TCFA and, indeed, plaques of other morphologies may also give rise to thrombotic events[5]. For example, in the *Providing Regional Observations to Study Predictors of Events in the Coronary Tree* (PROSPECT) study, only ~5% of thin-capped plaques as defined by virtual histology caused coronary events during a 3.4-year follow-up period[6]. As longitudinal intravascular imaging studies (such as PROSPECT) enrolled higher risk patients, we could observed that thin-capped plaques in lower risk populations may cause even fewer thrombotic events. Thus, the vast majority of so-called 'vulnerable plaques' does not exhibit clinical instability and seldom provokes ACS. Moreover, the consequences of a plaque disruption depend not only on the 'solid state' of the atheroma itself, but also on the fluid phase of blood (the concentration of fibrinogen, of endogenous inhibitors of fibrinolysis or pro-coagulant microparticles)[5,7].

In their article, Peter Libby and Gerard Pasterkamp brought up in front of us the challenges to the concept of 'vulnerable plaque', things that, indeed, are observed for quite some time in real life:
- thin-capped, lipid-rich atheromas are not solitary, rather often multiple and affect several arterial beds in the same individual;
- thin-capped, lipid-rich atheromas most often persist for years without causing a clinical event;
- the risk profile and demographics of ACS patients are shifting worldwide (global burden, younger patients, more women, more insulin resistance or diabetes, more hypertriglyceridaemia and less low-density lipoprotein excess);
- statin treatment and other preventive measures have begun to modify atherosclerotic disease;
- STEMI wanes as NSTEMI waxes;
- plaque rupture declines as a cause of acute coronary syndromes, while superficial erosion appears on the rise;

- plaques underlying cerebrovascular events reveal more 'stable' fibrous characteristics compared with that 10 years ago[5].

The fact is that the character of human plaques is changing in the statin era: they are getting less fatty and less "inflamed".

And, beside this changing in plaque's character, are we witnessing a shift in dominant mechanism of thrombosis in ACS? "Is the dominant mechanism of coronary thrombosis shifting from plaque rupture to superficial erosion?", as Libby and Pasterkamp rise the question? There are, indeed, a lot of autopsy studies on culprit lesions of ACS revealing that the rupture of the fibrous cap is more commonly accounted for fatal AMI than superficial erosion. Also, data from several leading pathologists have identified superficial erosion as a cause of ACS and highlighted the characteristics of lesions associated with fatal erosion that actually contrast quite starkly with those attributed to ruptured plaques.8 Opposed to lesions associated with plaque rupture, those that underlie superficial erosion do not have thin fibrous caps, harbour fewer inflammatory cells and they lack large lipid pools. Lesions that cause superficial erosion accumulate abundant extracellular matrix, notably proteoglycan and glycosaminoglycans.[9] This superficial erosion occurs more commonly in women, in individuals with diabetes and the elderly (population with more NSTEMI). As noted, lipid lowering treatment, in particular with statins, and perhaps less smoking, may modify the characteristics of the atherosclerotic plaque in a way that thickens the fibrous cap, reduces lipid accumulation, dispels inflammation and shrinks the volume of the lipid core. These morphologic changes should lead to stabilization of the plaques, reducing their risk of rupture. So, do statins and other current treatments reduce plaque rupture as the main cause of ACS?

Are we witnessing a shift towards superficial erosion vs rupture as a mechanism of thrombosis that contributes to the decline in STEMI and concurrent rise in NSTEMI? We already have some data that favour this hypothesis.

On one hand, we have the plaque erosion with it's characteristics:
- poor lipid content;
- proteoglycan and glycosaminoglycan rich;
- non-fibrillar collagen breakdown;
- few inflammatory cells;
- endothelial cells apoptosis;
- secondary neutrophil involvement;
- high triglycerides and
- female predominance.

Most often, plaques with superficial erosions do not, by themselves, cause critical obstruction. In such cases, the coronary obstructions are precipitated largely by the thrombi that develop on the dysfunctional intima. Based on autopsy findings in patients who died suddenly, endothelial plaque erosion may occur in as many as 40% of patients with fatal coronary thrombi[10]. Kubo et al. characterized these lesions by optical coherence tomography (OCT) and reported that they are characterized by loss of endothelial lining with intimal tears[3,11].

On the other hand, already known data on plaque rupture;
- rich lipid content;
- poor collagen and thin fibrous cap;
- interstitial collagen breakdown;
- abundant inflammation;
- SMC apoptosis;
- predominance of macrophages;
- high LDL- cholesterol and
- male predominance.

Contemporary optical coherence tomography studies have shown not only a growing proportion of ACS due to erosion vs fibrous cap rupture, but also provide preliminary evidence that erosion associates more frequently with NSTEMI than STEMI[12,13]. Coronary instability is assumed to be the result of plaque erosion if there is no continuity between the thrombus and the necrotic core and the thrombus is in direct contact with the fibrointimal plaque[14]. On OCT analysis, plaque erosion shows evidence of thrombi, irregular luminal surface, no evidence of cap rupture (in multiple adjacent frames), neutrophil activation playing an important role here. There is, also, a higher systemic myeloperoxidase level as compared with levels in patients exhibiting plaque rupture[15]. In postmortem coronary specimens, luminal thrombi superimposed on eroded plaques contained a higher density of myeloperoxidase (MPO)-positive cells than thrombi superimposed on ruptured plaques[16]. More, accumulation of hyaluronan and expression of CD44 along the plaque/thrombus interface of eroded plaques may promote de-endothelialization, resulting in CD44-dependent platelet adhesion and subsequent thrombus formation, in part mediated by a direct action of hyaluronan on fibrin polymerization. Furthermore, accumulation of hyaluronan in eroded plaques may promote CD44-dependent adhesion and accumulation of circulating

neutrophils and MPO-expressing monocytes, which in turn may enhance endothelial cell death and promote thrombus formation. MPO, released by neutrophils, catalyzes the formation of MPO-derived reactive species (MDRS), such as hypochlorous acid (HOCl), using chloride, thiocyanate or nitric oxide (NO) as the substrate and hydrogen peroxide as the cosubstrate. MDRS are responsible for consuming NO, which may result in impaired vasodilation, oxidation of LDL and high-density lipoprotein, activation of MMPs, oxidation of proteoglycans and glycosaminoglycans and apoptosis of endothelial cells. Furthermore, activated neutrophils shed microparticles, which may transfer tissue factor into platelets, thus contributing to thrombosis. Tissue factor expression and activation is also induced by MDRS and oxLDL[17]. MPO may also have a role in thrombus growth[18,19].

So, we already saw that eroded plaques exhibit particular morphological features that contrast with the characteristics of the lesions prone to rupture: the intima of eroded plaques typically has a discontinuous endothelial layer, contains abundant SMC and proteoglycans/glycosaminoglycans (in particular hyaluronic acid and versican) and few macrophages[10]. Disruption of the endothelial layer very likely contributes to acute thrombotic complications. And there is evidence that induction of endothelial apoptosis in vivo drives endothelial denudation and thrombus formation[20]. More, endothelial cell apoptosis in human plaques associates frequently with oscillatory shear stress downstream of plaques, where plaque erosions tend to occur[21].

In an article published in *European Heart Journal* in 2015, Thibaut Quillard and his co-workers described two important key-factors involved in plaque erosion: the initial endothelial injury, mediated by TLR2 (toll-like receptor-2), followed by death and/or sloughing/desquamation at this level, neutrophils recruited to the scene mediating a 'second hit' by amplifying, sustaining and propagating the local processes that promote endothelial injury. As thrombosis and coagulation provoked by local tissue factor generation by dying endothelial cells and contact with the subendothelial matrix occurs, granulocytes can become trapped in the fibrin trands and form NET's (neutrophil extracellular traps), as observed by the authors in the human specimens studied[22].

As mentioned by Quillard, breaches in the integrity of the arterial intimal endothelium, normally, undergo rapid repair by coverage by adjacent endothelial cells. In their study, they found that TLR2 activation impaired repair of injury to an endothelial monolayer in vitro. Once a small patch of endothelium desquamates, recruitment and activation of platelets and granulocytes can ensue, favouring formation of NET's. PMNs can markedly potentiate the injurious effects of TLR2 ligation, with subsequent amplification of the local intimal damage and possible promotion of thrombosis associated with superficial erosion. The observations that hyaluronan triggers IL-8 release by EC23 and CD44–hyaluronan interactions promote neutrophil recruitment and adhesion, tighten the links between PMN and superficial erosion[24].

So, this study documented a particularly strong correlation between apoptotic EC and the presence of NETs in human plaques with a superficial erosion-like morphology. This observation indicates that this mechanism of endothelial apoptosis applies particularly to superficial erosion, but not in 'rupture-prone' lesions[22].

So, we have in front of us some major differences between eroded and ruptured plaques (or between the plaques prone to erosion and those prone to rupture): it seems like neutrophils participate predominently in the propagation of superficial erosion, while there is a lot of evidence supporting the pathogenic key role of monocytes/macrophages in plaque rupture; apoptosis of SMC may prevail in formation of thin-capped atheromas, while endothelial cells apoptosis appears more critical in superficial erosion; fibrillar collagenases participate in plaque rupture, while non-fibrillar collagenases in superficial erosion; accumulation of proteoglycan, rather than paucity of interstitial collagen, characterize the lesions complicated by superficial erosion[22].

But, on the other hand, as mentioned above, the consequences of a plaque disruption depend not only on the 'solid state' of the atheroma itself, but also on other factors, including inflammation, and several studies have shown that patients with ACS in whom obstructive atherosclerosis is associated with elevated levels of CRP (C-reactive protein) or other markers of inflammation have a worse outcome than patients with a similar severity of coronary atherosclerosis, but normal levels of inflammatory markers[25-27]. In the former, reassessment of the inflammatory status after discharge may help in the identification of patients at higher risk of recurrence of coronary instability. Although the assessment of the inflammatory status is currently based on biomarkers only, recently developed imaging techniques able to monitor inflammatory

cell activity in atherosclerotic plaques might prove to be more predictive than biomarkers[28].

But, as mentioned above, we are interested not only in the 'solid state' of the atheroma itself, but, it's also important what happens with the fluid phase of blood (concentration of fibrinogen, of endogenous inhibitors of fibrinolysis, pro-coagulant microparticles, endothelial shear stress, etc.).

As known, endothelial shear stress (ESS) influences the vessel dimensions and wall composition in different ways during the progression of atherosclerotic plaque development, especially of obstructive high-risk plaques, that alters the initially low local haemodynamic environment by creating high ESS conditions in the neck of the plaque and low ESS in downstream plaque regions and potentially in the upstream shoulder, suggesting the dynamic interplay between local ESS, plaque development and vascular remodelling. The sustained low ESS environment represents a key mediator of destabilization of non-obstructive high-risk plaques, by promoting excessive inflammation and matrix degradation, leading to plaque fragility, erosion or rupture. In contrast, obstructive highrisk plaques can be destabilized at the most stenotic site under the influence of high ESS conditions, triggering molecular pathways that weaken the plaque, or at the upstream shoulder and downstream parts exposed to low ESS environments. Indeed, as plaques are growing, the local ESS changes in magnitude, direction and spatial distribution[29,30]. Thus, a developing plaque itself can modify the local ESS milieu in specific parts of a lesion (or near it). Depending on the shape of the plaque, lumen narrowing due to a stenotic lesion results in a heterogeneous ESS distribution, with potentially relative low ESS occurring in the upstream shoulder of the plaque, high ESS at the most stenotic site of the plaque and low oscillatory ESS at the downstream shoulder. The downstream plaque region exposed to low and oscillatory ESS contains significantly more SMC and less inflammation, while the upstream shoulder region, potentially exposed to low ESS, appears more inflamed, containing a high number of macrophages and expressing higher gelatinolytic activity[31]. This relates to the observations in carotid and coronary arteries that ruptured sites occur predominantly at upstream locations, whereas the downstream parts are prone to plaque growth.

As many studies have shown, low ESS increases the expression of matrix-metalloproteinases (MMPs) and cathepsins. Also, animal studies have demonstrated that low ESS induces elastolytic activity of elastases (MMP-2, -9, -12 and cathepsins K, L and S) and collagenases (MMP-1, -8 and -13). Collagenases degrade interstitial collagen in the fibrous cap, thereby promoting fibrous cap thinning, whereas elastases break down elastin fibres in the internal elastic lamina, facilitating the migration of macrophages from the intima to media, promoting wall expansion, as well as the migration of SMC from the media to intima, promoting plaque growth. Low ESS has been shown, also, to induce SMC apoptosis and de-differentiation in the fibrous cap, leading to reduced production of extracellular matrix in the cap. These in vivo investigations clearly demonstrated that low ESS-induced extracellular matrix degradation and reduced production promotes matrix remodelling, internal elastic lamina degradation and thinning of the fibrous cap, all of which are critical steps in the development of a high-risk plaque (erosion or rupture-prone)[32].

Present and future treatment options

In patients with ACS in whom plaque fissure is not associated with systemic inflammation, anatomic features of the atherosclerotic plaque are important in determining coronary instability. An obvious target in these patients is plaque stabilization as achieved by intensive statin treatment[25].

Statin treatment induces favorable plaque morphologic changes with an increase in fibrous cap thickness and decreases in both percentage plaque and lipid volume indexes, as shown by Kousuke Hattori et al. during a prospective trial with serial OCT, grayscale and IB-IVUS of non-target lesions, performed in 42 patients undergoing elective coronary intervention, from whom 26 received 4mg of Pitavastatin, 16 subjects, who refused statin treatment, followed dietary modification alone; follow-up imaging was performed after a median interval of 9 months. Treatment with Pitavastatin induced significant plaque regression and, by decreasing plaque lipid content and increasing plaque fibrous cap thickness, inducing thus plaque stabilization[33].

And, let's not forget, we have the „old" data from JUPITER trial (*Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein*): statin therapy prevented cardiovascular events and mortality not only in patients with hyperlipidaemia, but also in those with normal LDL-cholesterol level and elevated CRP level (≥2.0 mg/L), at the same time reducing serum CRP level[27]. Based on the statin trials, Paul Ridker and Eugene Braunwald suggested that cholesterol lowering per se is associated with some anti-inflammatory effects[34-36]:

a) they increase endothelial nitric oxide synthase expression and thrombomodulin via the Kruppel like factor 2 (KLF-2), a transcription factor participating in the regulation of inflammatory and proliferative processes[35];

b) they act by inhibiting formation of proinflammatory helper Th-1 lymphocytes and promote formation of anti-inflammatory Th-2 lymphocytes, regulating the course of the inflammatory respons[36];

c) they also induce inhibition of proinflammatory factors, such as NF-kB and activator protein 1 (AP-1), leading to a reduced expression of vascular cellular adhesion molecule 1 (VCAM-1), E-selectin, P-selectin and tissue factor[36].

Inhibitors of phospholipase A2 represent another class of drugs that might help in plaque stabilization. Another important target to promote plaque stabilization is enhancement of cholesterol efflux[37]. Among patients in whom plaque fissure is not associated with systemic inflammation and in whom ACS occurs in the absence of environmental, physical or emotional triggers, more needs to be learned about the mechanisms modulating cholesterol crystallization, including the inflammasome pathway activated by cholesterol crystals, in order to identify new therapeutic targets[2].

In patients with plaque erosion, the mechanism of inflammation is probably an intense local thrombogenic stimulus, so, in this subset of patients, a potent antithrombotic treatment perhaps based on double antiaggregation and an oral anticoagulant might be the treatment of choice, but this approach needs to be tested in prospective studies[2]. Just one example, reffering to Rivaroxaban: in mice, the use of small doses of Rivaroxaban resulted in plaque stabilisation by increasing thickness of the fibrous cap and reduced plasma IL-6 and TNF-a levels[38].

CONCLUSION

We have to keep in mind that superficial erosion of coronary atheromas causes approximately 20 to 25% of cases of fatal AMI and this anatomical substrate for coronary thrombosis occurs more frequently in women than in men and in persons with certain risk factors (such as hypertriglyceridemia or diabetes). Many lesions that cause coronary thrombosis because of superficial erosion lack prominent inflammatory infiltrates; such plaques exhibit proteoglycan accumulation. Apoptosis of endothelial cells could contribute to their desquamation, while oxidative stress can promote en-

dothelial apoptosis. As these cells undergo apoptosis, they produce the procoagulant tissue factor. Oxidative species may initiate or propagate endothelial cell loss and local thrombosis in coronary arteries. Endothelial cells can also express proteinases that may sever their tethers to the underlying basement membrane.

And, as Peter Libby said[39], the mechanisms of superficial erosion merit attention in future investigations, because they are much less well understood than the mechanisms underlying the fracture of the plaque's fibrous cap.

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