How to study the effects of inflammation on coronary vasomotion and their clinical relevance

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In patients with acute coronary syndromes systemic inflammation is associated with an enhanced vasoreactivity of the culprit coronary lesion. In the complex scenario of the mechanisms responsible for myocardial ischemia, the increased coronary vasoreactivity at the site of the culprit lesion may represent an important pathogenetic factor by limiting coronary blood flow. Systemic inflammation and epicardial vessel vasomotion can be easily measured in humans although, at present, the clinical relevance of such association has not been assessed in clinical trial. In the future, the development of drugs capable of blocking inflammatory molecules, in particular C-reactive protein and endothelin-1, will provide new tools to establish whether inflammation directly contributes to the pathogenesis of the enhanced coronary vasoreactivity and, more importantly, whether these drugs will be capable of positively affecting the prognosis of patients with acute coronary syndromes.

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Inflammation and acute coronary syndromes

Several studies carried out in the last decade have consistently shown that inflammation plays a crucial role in the activation of coronary atherosclerotic lesions leading to coronary thrombosis, the pathophysiological substrate of acute coronary syndromes[1]. Indeed, inflammation at the site of the active coronary plaque has several detrimental consequences[2]: 1) the activation of the endothelium, transforming its antiadhesive and anticoagulant properties into adhesive and procoagulant propensity; 2) the reduction of matrix synthesis and the increase of its degradation by metalloproteinases, thus favoring plaque rupture; 3) the stimulus for the formation of fragile and prone to hemorrhage microvessels in the plaque ("neoangiogenesis") which serve as a portal for leukocytes trafficking, and finally 4) the release of powerful constrictors by activated leukocytes, endothelium, smooth muscle cells and platelets.

Increased coronary vasoreactivity in acute coronary syndromes

In 1994 Bogaty et al.[3] observed that the culprit lesion of patients with unstable angina exhibited an enhanced vasoconstrictor response to cold pressor and exercise test in comparison with the culprit lesion of patients with stable angina. More recently we have confirmed these findings and observed that patients with unstable angina, compared to those with stable angina, present also an increased resting tone at the site of the culprit lesion[4,5]. Of note, in all studies, the abnormal coronary vasomotion was observed only at the level of the culprit lesion and not at the level of uninvolved proximal and distal coronary segments thus supporting the concept that the abnormal vasoreactivity is a local plaque-related phenomenon.

Inflammation and abnormal vasomotion

Although the mechanisms responsible for the increased vasoreactivity of the unstable atherosclerotic plaque are still poorly understood, inflammatory mechanisms are likely to play a relevant role[2]. Recently, the relation between inflammation and abnormal vasoreactivity of the systemic and coronary circulation has been systematically investigated. Fichtlscherer et al.[6] found that elevated C-reactive protein (CRP) levels are independent predictors of endothelial dysfunction in patients with coronary artery disease. In particular, patients with

elevated CRP levels, compared to those with normal CRP levels, exhibited a reduced forearm vasodilator response to acetylcholine. Most important, normalization of elevated CRP levels over time was associated with a normalization of endothelium-mediated blood flow responses. These findings have been confirmed by Hingorani et al.[7], who showed that a mild inflammatory reaction induced by *Salmonella typhi* vaccine impairs forearm endothelium-dependent vasodilation. We have recently investigated the relation between systemic inflammation and coronary vasoreactivity at the site of the culprit lesion in patients with coronary artery disease[5]. We found that in patients with unstable angina elevated CRP levels are independently associated with enhanced vasoreactivity of the culprit lesion. Indeed, unstable patients with elevated CRP levels exhibited both a greater dilation of the culprit lesion after intracoronary nitroglycerin (an endothelium-independent stimulus) and a greater constriction of the culprit lesion during cold pressor test (an endothelium-dependent stimulus), thus suggesting in these patients both an enhanced resting tone of the culprit lesion and an alteration of endothelium-dependent vasodilation. Interestingly, in patients with stable angina also CRP levels were independently associated with enhanced vasoreactivity of the culprit lesion. These findings are in keeping with the results of several previous investigations showing an independent prognostic relevance of CRP for the risk of coronary artery disease not only in patients with unstable angina but also in apparently healthy men[8,9] and in patients with stable angina[10].

Causes for the enhanced vasoreactivity of the active coronary plaque

Inflammatory processes within the plaque cause the production and release of a number of potent vasoconstrictors by activated inflammatory cells (macrophage, neutrophils and lymphocytes), smooth muscle cells, endothelial cells, and platelets. Furthermore, plaque inflammation may affect endothelial vasodilator capability by inhibiting the production of nitric oxide by superoxide anion whose production is augmented in the activated plaque[2]. Substances such as thrombin, serotonin, angiotensin II, thromboxane A_2 and endothelin-1 (ET-1) released at the site of the active atherosclerotic plaque might all cause intense coronary vasoconstriction. Among vasoconstrictors, much attention has been dedicated to ET-1 which belongs to a family of peptides that are potent constrictors of vascular smooth muscle[11]. In addition, ET-1 markedly potentiates the constrictor effects of other vasoconstrictors such as catecholamine, serotonin and angiotensin II. Its release is stimulated by thrombin and inflammatory factors such as interleukin-1[12]. ET-1 is produced not only by endothelial cells but also by macrophages, polymorphonuclear leukocytes and smooth muscle cells activated by inflammatory mediators[12]. In an *in vitro* study, Zeiher et al.[13] evaluated the ET-1-like immunoreactivity at the site of coronary atherosclerotic lesions obtained by directional coronary atherectomy from patients with stable angina and patients with crescendo and postinfarction angina. They found that ET-1 staining grade was significantly greater in patients with acute coronary syndromes compared to that observed in atherosclerotic plaque tissue obtained from patients with stable angina. Importantly, ET-1 immunostaining was most prominent in the areas with evidence of infiltration by macrophages whose key role in the transition from stable to unstable lesions is well established. The potential role of ET-1 for the increased vasoreactivity of the culprit lesion in patients with unstable angina has been further evaluated in a recent study in which we observed that coronary artery stent implantation at the site of the culprit atherosclerotic lesion was followed by a detectable local increase of serum levels of ET-1, which was significantly greater at the site of the unstable than at the site of the stable plaque[4]. Thus, a local enhanced release of ET-1 might be responsible, at least in part, for the enhanced vasoreactivity of the culprit lesion in patients with unstable angina.

Assessment of systemic inflammation: the pivotal role of C-reactive protein

Among the numerous systemic markers of inflammation, CRP, the prototype of the acute phase reactants, has so far received the greatest attention[14]. Its independent prognostic role in a variety of cardiovascular conditions has been repeatedly emphasized. Baseline levels of CRP in apparently healthy persons[8], in subjects with cardiovascular risk factors[9] and in patients with stable angina[10] represent an independent risk factor for future cardiovascular events. Furthermore, high CRP levels in patients with unstable angina[15] and myocardial infarction[16] have been associated with a worse prognosis. Finally, persistently elevated CRP plasma levels after coronary surgery[17] and coronary artery stent implantation[18,19] are predictive of postprocedural complications and in-stent restenosis. Currently, the availability of standardized high-sensitive assays for CRP determination provides accurate measurements of this inflammatory marker which is now included in the routine blood testing in many centers[14,20].

Assessment of epicardial vessel vasomotion

At present, quantitative coronary angiography represents the only reliable method to evaluate epicardial vessel vasomotion[21]. Alternatively, the new generation of multistrate computed tomography appears promising for the noninvasive evaluation of epicardial coronary vessels but it is still far to be applicable in the rou-

tine clinical setting. Quantitative angiographic analysis is usually made by the use of standardized automated edge-detection system, which allows the diameters to be measured as absolute values. Minimal luminal diameter of the culprit lesion, reference segment diameter, and percent diameter stenosis are directly obtained with this analysis system. Modern analysis systems utilize dedicated softwares capable of automatically dividing the coronary vessel into contiguous 5-mm segments and determine the diameter of each segment. All measurements are performed using an end-diastolic frame and should be obtained for the angiograms taken at baseline and during the pharmacological or physical challenge. Care should be taken to choose identical projections of the target lesion for all assessed angiograms.

Several vasoactive agents have been used for the assessment of epicardial vasomotion. Endothelium-dependent coronary vasodilation can be interrogated by using both pharmacological agents like acetylcholine and substance P and physical challenge, such as cold pressor test[22]. For the assessment of endothelium-independent vasodilation, nitroglycerin and sodium nitroprusside may be administered as an intracoronary bolus.

Clinical relevance of the effects of inflammation on coronary vasomotion

Although it is well established that a systemic inflammatory status is associated with a worse prognosis in patients with ischemic heart disease and it appears intuitive that an enhanced coronary vasoreactivity may aggravate or even precipitate myocardial ischemia by limiting coronary blood flow, the clinical relevance of such association has not been systematically investigated in clinical studies. It might well be that in selected subgroups of patients with persistent ischemia and symptoms despite massive anti-ischemic therapy a high inflammatory systemic activation might induce coronary instability because of enhanced coronary vasomotion. Indeed, the increased vasoconstrictor tone and the enhanced vasoconstrictor response of the active unstable plaque may explain the resistance to systemic vasodilators observed in some patients with acute coronary syndromes. In the future, the development of specific anti-inflammatory drugs will provide the tools to determine whether inflammation is directly involved in the pathogenesis of enhanced coronary vasoreactivity and more importantly, whether these drugs will be capable of positively affecting the prognosis of patients with acute coronary syndromes. In this context, the utilization of ET-1 inhibitors, which have been shown to have therapeutical potential in early clinical studies, will determine whether these new pharmacological agents have the capability of reducing coronary vasomotion and possibly coronary morbility and mortality in acute coronary syndromes.

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