CORONARY INFLAMMATION. WHY SEARCHING, HOW TO IDENTIFY AND TREAT IT

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Abstract

In a process of personalized medicine, there is need to accurately identify patients at high risk of events. Nowdays systemic inflammation can be detected by measuring blood inflammatory markers but there is lack of a more specific assessment of coronary inflammations. The use of imaging modalities (either invasive or non-invasive), seems a reasonable solution to be applied in the future. In this scenario, OCT is the intracoronary imaging modality that may serve the scope of identifying vulnerable plaques with local aggregates of inflammatory cells. Future studies are needed to understand the impact of a more accurate assessment of coronary inflammation and the clinical effectiveness of strategies for switching it off.

Role of inflammation to promote growth of atherosclerosis and plaque distruption

Inflammation plays an important role in the development of atherosclerotic lesions. A variety of stimuli promote atherosclerosis, including increased LDL cholesterol in blood, exposure to tobacco, diabetes mellitus, hypertension, or rheological stress. Inflammatory cells have an established role in the growth of atherosclerotic lesions. Macrophages recognise and internalise ox-LDL to eventually become lipid-laden foam cells, the hallmark cellular component of atheromas. Infiltrating CD4-T cells have a role too, by interacting with ox-LDL and other antigens [1].

Cytokines secreted by inflammatory cells stimulate smooth muscle cells migration whilst macrophages produce metalloproteases that lead to fibrous cap rupture [1]. The necrotic debris of died macrophages and smooth muscle cells help to continue the inflammatory process. The inflammatory response can

also directly activate platelets and promote thrombus formation at the surface of complicated coronary plaques.

Relationship between inflammation and acute coronary syndromes

Acute Coronary Syndrome (ACS) tends to occur in presence of high concentrations of inflammatory markers in the blood, such as C-Reactive Protein (CRP), neutrophil myeloperoxidase, procalcitonin, and white blood cells [1]. There are convincing data on the link between acute infections and their direct inflammatory effects on atherosclerotic plaques. People dying of acute systemic infections have a substantially higher number of macrophages and T cells in the coronary adventitia and periadventitial fat, than people who died without infection [1,2]. Furthermore, an increased morbility and mortality related to acute coronary syndromes has been observed during influenza epidemics [1,2]. According to a large histology study on 34.000 autopsies by Madjid et al. [2], myocardial infarction is 30% more likely to happen during influenza season. Other observational studies further support this association. Kwong et al. [3] studied 364 hospitalizations for acute myocardial infarction that occurred within 1 year before and 1 year after a positive test result for influenza. Incidence ratios for acute myocardial infarction within 7 days after detection of influenza B and influenza A were significantly higher.

Consistently, a large retrospective study [4] showed that early treatment of influenza in patients with established cardiovascular disease was associated with a 60% reduction in the risk of recurrent cardiovascular events. Also, vaccination against influenza may reduce the risk of acute coronary syndromes.

Utility of CRP as an inflammatory marker

The role of inflammatory markers in cardiovascular risk assessment and the development of cardiovascular disease has been a topic of discussion for nearly two decades. Inflammatory markers, including high-sensitivity C-Reactive Protein (hs-CRP), are not yet considered applicable for routine assessment due to lack of measurement standardization, consistency in epidemiological findings, and evidence for additional risk prediction. Despite this, in most of published studies hs-CRP surge is related to a worse clinical outcome in patients with ACS, stable coronary disease and previous percutaneous coronary intervention [5]. On the same note reduction of PCR values below the threshold level by means of statins and more recently of the anti-inflammatory drug Canakinumab [6], reduces significantly the risk of cardiovascular events.

On the other hand, CRP use to stratify the risk of cardiovascular events in primary prevention is still a debated issue. A major limitation of PCR titration resides in its low specificity for coronary artery disease as many inflammatory pathologies can increase CRP values. In a recent study on the prevalence of CAD in an indigenous population, the Tsimane aborigines, with the lowest reported levels of CAD in the world high levels of CRP, related environmental exposure to infections, were found [7].

The role of PCR itself in the genesis of atherosclerosis and occurrence of acute events is still unclear and there is ongoing debate as to whether CRP

should be more than just a disease marker. Based on several reports [3] hs-CRP may have a role in the causation of atherosclerosis as a number of in vitro and animal studies suggest a pro-atherogenic role for CRP.

At the current stage there is some consensus that CRP testing might improve risk stratification, among intermediate cardiovascular risk patients, as previously reported [5].

Systemic versus localized inflammation

What seems rather obvious is that CRP increase does not reflect the high inflammatory contents of a single vulnerable or disrupted plaque causing an acute ischemic event. Elevation in the baseline concentration of CRP is induced by proinflammatory cytokines IL-1, IL-6, and IL-17 in the liver, reflecting therefore a possible generalized widespread inflammation due to atherosclerosis.

Buffon et al. [8,9] showed a higher widespread neutrophil activation in patients with ACS as compared with stable patients regardless of the location of the culprit coronary lesion. Data from Buffon are in line with histology post mortem data obtained in patients with unstable angina. Arbustini et al. found multiple plaques with inflammatory-cell infiltrates and with a high content of proinflammatory cytokines [10].

Other pathology and IVUS studies [11,12] identified signs of plaque fissure in many non-culprit sites. Ge et al. showed in an IVUS study that signs of ulceration in remote non ACS culprit sites are uncommon findings [13]. Such findings gave strength to the concept of pan vascular disease, with simultaneous destabilization (rupture) of multiple plaques and tackled the concept of plaque vulnerability, discouraging any preventive strategy based on the trans-catheter treatment of interventional lesions. However, plaque ulceration may persist for months or years as showed by serial studied with OCT [14,15] and fresh acute thrombosis in remote non culprit ACS sites is a rare finding [16]. In other word, despite presence of multiple ulceration in a coronary tree, the simultaneous plaque rupture seems a rare event [16].

Recent findings highlighted the role of local inflammation, showing that, even in a contest of widespread inflammatory arousal, culprit plaques of ACS have a higher inflammatory content.

Narula et al. [17] showed in a post mortem study that macrophage infiltration was significantly higher at the lesion site deemed responsible for the sudden death as compared to vulnerable non culprit plaque located in the same artery 0.31 ± 0.36 mm^2 vs. 0.53 ± 0.44 mm^2; $p < 0.001$. This finding has been then confirmed by a study carried on with OCT and IVUS-NIRS. Macrophages along with other features of vulnerability were more often detected at the site of culprit ACS lesions [18]. These finding may be in support of the search of vulnerable plaques, containing inflammatory cells.

Imaging detection of inflammation

Detection of coronary inflammation is not a simple task. FDG PET has certainly some potentials. FDG is a radio-labelled glucose analogue which

competes with glucose for transport across the sarcolemma and phosphorylation by hexokinase and is avidly accumulated by metabolically active cells. Previous studies have shown that the FDG uptake in the carotid arteries is associated with plaque macrophage infiltration and occurrence of cerebrovascular ischemic events [19,20].

MRI is a high-resolution non-invasive imaging modality. The combination of multiple MR sequences can identify the main features of atherosclerotic plaques, such as the fibrous cap, LRNC, intra-plaque haemorrhage, neovascularization, and signs of inflammation [21].

Two MRI strategies have been used to detect macrophage infiltration:

a) dynamic kinetics of tissue enhancement after gadolinium administration (DCE);
b) Ultra-Small super-Paramagnetic particles of Iron Oxide (USPIO) targeting macrophages in vivo.

Unfortunately, both FDG PET and MRI at the current stage of development are not suited for coronary assessment. Small vessel size of coronary arteries and cardiac motion are the main obstacle to plaque assessment with either MRI and PET, and confine these two imaging technique to peripheral studies. CT on the other hand is largely adopted to study the coronary arteries. Unfortunately, CT has not the resolution to detect inflammatory cells, although preliminary experiences have been done in this regard, using targeted nanoparticle contrast agents [22]. In atherosclerotic mice, spectral CT enabled detection of intra-plaque inflammation after injection of gold-labelled high-density lipoprotein nanoparticles designed to target activated macrophages [23].

The advent of high-resolution intracoronary imaging strategies, have opened a new chapter in plaque characterization. OCT is so far the only commercially available intracoronary technique that is able to characterize plaques and study inflammation. In the multicentre prospective CLIMA registry on plaque vulnerability [16], we showed for the first time that an association exists between macrophages presence and higher risk of cardiac events at follow-up. Macrophage clusters were observed in about half of cases, and were related to the risk of adverse event (HR 2.66). More importantly, macrophage plaque infiltration further improved the classification of high-risk plaque phenotype; in fact, when include on the top of MLA, FCT and lipid arc extension the risk of future adverse events increased from HR 5.40 to HR 7.54.

Intravascular Near-Infrared Fluorescence (NIRF) using targeted molecular agents is a novel promising solution, to study plaque vulnerability and coronary inflammation [24]. Detection of fluorescence from naturally occurring molecules also known as autofluorescence, is closer to clinical application because it can be detected without the administration of exogenous agents that are not yet approved for human use. An autofluorescence-OCT probe has been tested in human plaques ex vivo to identify and showed potential to visualize elastin, collagen, and macrophage accumulation [24].

Therapeutical implication

The CANTOS trial [6] can be waived as an innovative studies promoting a novel approach of personalized medicine. In patients with previous myocardial

infarction, high-sensitivity C-reactive protein level of 2 mg and normal LDL level (<70 mg/dL), canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, at a dose of 150 mg every 3 months, led to a significant reduction of the primary efficacy endpoint: nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death at 48 months.

Based on the CANTOS results, 6 patients on statins and residual inflammatory risk as assessed by means of a high-sensitivity CRP >2 mg/l at baseline have a high risk of future cardiac events, comparable to that of statin-treated patients with suboptimal cholesterol LDL level. The inhibition of interleukin-1β by means of canakinumab, which is only one of many potential anti-inflammatory pathways, open new perspectives, showing that a selective inhibition of the inflammatory pathway may be beneficial in reducing cardiovascular risk.

In a process of personalized medicine, there is need to accurately identify patients at high risk of events, to be treated with potent statins or anti-inflammatory drugs. Perhaps in the next future a more specific assessment of coronary inflammations, possibly obtained with imaging modalities (either invasive or non-invasive), will better select patients at risk of events. In this scenario, in the setting of secondary prevention, OCT may serve the scope of identifying vulnerable plaques with local aggregates of inflammatory cells. Future studies are needed to understand the clinical effectiveness of strategies based on invasive coronary assessment.

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