REVIEW ARTICLE

Inflammation in Acute Coronary Syndromes: Mechanisms and Clinical Implications

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Inflammation plays a pivotal role in the pathogenesis of atherosclerosis and its complications. In particular, atherosclerosis is an active process and the inflammatory component appears to be particularly correlated with the development of acute coronary syndromes (ACS). Accumulating data demonstrate that in ACS, elevated levels of circulating inflammatory markers, such as C-reactive protein, predict an unfavorable cardiovascular outcome. A better knowledge of the molecular and cellular mechanisms of inflammation might not only further improve prognostic stratification but also allow us to identify novel therapeutic targets. The present review summarizes the mechanisms of the inflammatory response in ACS, its clinical implications, and the potential treatment strategies to contrast this phenomenon.

Key words: *Atherosclerosis. Acute coronary syndromes. Inflammation. C-reactive protein.*

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La inflamación en los síndromes coronarios agudos: mecanismos e implicaciones clínicas

La inflamación desempeña un papel fundamental en la patogenia de la aterosclerosis y de sus complicaciones. La aterosclerosis es un proceso activo y el componente inflamatorio parece estar particularmente correlacionado con el desarrollo de los síndromes coronarios agudos. Los datos que se han ido recogiendo demuestran que, en los síndromes coronarios agudos, las concentraciones elevadas de marcadores circulantes de inflamación, como la proteína C reactiva, predicen una respuesta cardiovascular desfavorable. Aumentar el conocimiento de los mecanismos moleculares y celulares de la inflamación puede no solamente redundar en una mejor estratificación pronóstica, sino también permitir la identificación de nuevas dianas terapéuticas. En esta revisión se resumen los mecanismos de la respuesta inflamatoria en los síndromes coronarios agudos, sus implicaciones clínicas y las potenciales estrategias terapéuticas para contrarrestar este fenómeno.

Palabras clave: *Aterosclerosis. Síndromes coronarios agudos. Inflamación. Proteína C reactiva.*

INTRODUCTION

In the last years a growing body of evidence has demonstrated that inflammation plays a pivotal role in the pathogenesis of atherosclerosis and its complications and nowadays atherosclerosis is considered at all effects "an inflammatory disease."[1-4] Accumulating data demonstrate that elevated levels of circulating inflammatory markers predict an unfavorable cardiovascular outcome in asymptomatic subjects, in patients with stable ischemic heart disease and in patients with acute coronary syndromes (ACS).[5-25] Improved knowledge of the molecular and cellular mechanisms of inflammation might not only further improve prognostic stratification but also allow us to identify novel therapeutic targets.[4,26] The present re-

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view summarizes the mechanisms of the inflammatory response in ACS, its clinical implications, and the potential treatment strategies to differentiate this phenomenon.

INFLAMMATION AND ATHEROGENESIS

Triggers of inflammation in atherogenesis include traditional risk factors such as hypercholesterolemia,[27-36] hypertension,[37-42] diabetes,[43,44] obesity,[45] homocysteine,[46-51] cigarette smoking,[52-59] infections.[60-66] These atherogenetic stimuli provoke an injury to the arterial wall and, according to the "response to injury" theory described by Ross, atherosclerosis is the result of an excessive inflammatory-fibroproliferative response.[1,2] The inflammatory response not only promotes initiation of the atherosclerotic process, but also contributes to the subsequent growth of atheroma and the precipitation of acute thrombotic events.[1-4,67]

The normal arterial endothelium in contact with flowing blood resists firm adhesion of leucocytes, including blood monocytes.[68,69] Following inflammatory activation, the endothelial cells increase their expression of various leucocyte adhesion molecules allowing attachment and migration of monocytes and T lymphocytes between the endothelial cells into the arterial wall.[70-72] Various chemoattractants cytokines (chemokines) also participate in both monocyte and lymphocyte recruitment.[73-77] Monocytes once resident in the arterial wall acquire characteristics of tissue macrophages and of foam cells which secrete reactive oxygen species, pro-inflammatory cytokines, metalloproteinases (MMPs), growth factor, tissue factor, amplifying the local inflammatory process.[78-81] In the arterial wall T cells may interact with antigens such as oxidized-LDL and heat shock proteins (endogenous or microbial), leading to lymphocyte activation and cytokine production.[27,61,82,83] In particular, the T helper lymphocytes within the atheroma can polarize into those secreting pro-inflammatory cytokines (interleukin-1 [IL-1], tumor necrosis factor [TNF], interferon-γ (IFN-γ, known as T_H1 cells, or those secreting anti-inflammatory cytokines (IL-4, IL-10), known as T_H2 cells.[84] T_H1 cells producing IFN-γ, a pleiotropic cytokine involved in monocyte/macrophage activation, generally predominate in the atheroma.

In mature atherosclerotic plaques two different regions may be identified: the fibrous cap, rich in collagen fibers and smooth muscle cells, and the core, rich in foam cells, macrophages and cellular necrotic debris.[1-4] Macrophages may congregate in a central core in the typical atherosclerotic plaque where they can undergo apoptosis producing the "necrotic core" of the atherosclerotic lesion or release MMPs which degrade the extracellular matrix promoting plaque rupture.[85-88] This allows blood contact with tissue factor (TF), a potent pro-coagulant protein produced also by macrophages, promoting thrombotic complications of the atherosclerotic plaque.[67,78-80] Even in the absence of plaque fissuring, pro-inflammatory cytokines (IL-1, IL-6, TNF-α) may potentiate pro-coagulant properties of endothelial cells and neutrophils, thus contributing to thrombotic complications of the atherosclerotic plaque.[67,78-83]

In summary, atherosclerosis is a chronic process with an important active and ongoing inflammatory component. Inflammation plays an important role not only in "triggering" the atherosclerotic process, but also in promoting atherosclerotic plaque development and complications. Notably, the evolution of the disease is not uniform among individuals, probably because of individual differences in the inflammatory response to atherogenic stimuli. Individuals with a greater inflammatory response to atherogenic stimuli have a higher risk of developing clinical manifestations of atherosclerosis. Indeed, systemic markers of inflammation, such as C-reactive protein (CRP), are associated with a higher long-term risk of acute myocardial infarction, stroke or severe peripheral vascular disease. While the inflammatory triggers and mechanisms of the early phases of atherogenesis are relatively well known, the inflammatory triggers and mechanisms of acute thrombotic complications of atherosclerotic plaques are probably different and still largely unknown.

TRANSITION FROM STABLE TO UNSTABLE CORONARY SYNDROMES: CLINICAL AND POST-MORTEM OBSERVATIONS

It is still unclear why many patients with severe and extensive atherosclerosis remain stable for years without developing acute coronary syndromes (ACS), while others develop acute events as the first manifestation of ischemic heart disease in spite of less severe coronary atherosclerosis.[89,90] ACS are clinically characterized by a sudden onset, and by the possible recurrence of ischemic episodes over a period of days, weeks or months followed by the return to a stable or quiescent phase of ischemic heart disease.[91,92] Thus, the clinical presentation indicates that ACS are related to the waxing and waning of destabilizing stimuli. The clinical presentation and evolution, however, may vary considerably; such variability may reflect a different prevalence of underlying mechanisms of instability.[91,92] At one extreme there are patients with unheralded acute myocardial infarction (MI) who then remain asymptomatic for years. At the other extreme there are patients in whom MI is preceded by unstable angina for days or weeks who subsequently continue to develop recurrent episodes of instability and/or reinfarction during the fo-

llowing weeks or months in spite of state of the art treatment.[89,91,92]

It is worth noting, that in a sizeable proportion of patients ACS are associated with an inflammatory outburst detectable by the measurement of systemic markers of inflammation such as CRP. The prevalence of elevated CRP levels (>3 mg/L) in peripheral blood range from 70% in patients with severe unstable angina to nearly 100% in MI preceded by unstable angina, while this is found in less than 50% in MI not preceded by unstable angina and in less than 20% of patients with stable angina.[17,18,89,93]

Destabilizing stimuli, regardless of their nature, cause occlusive coronary thrombosis which is directly responsible for myocardial ischemia (Figure 1).[94] The most striking and distinctive postmortem feature of unstable angina compared to chronic stable angina is the frequent presence of non occlusive, mural coronary thrombi at the site of disrupted atherosclerotic plaques, occasionally with distal vessel embolization.[95-97] Mural thrombi are composed of platelets and fibrin and often represent outgrowths from the inside of an underlying fissured plaque. It is important to note that: *a)* thrombi are often composed of layers of different ages, which is indicative of thrombosis developing on separate occasions at intervals of days or weeks; *b)* in 25% to 50% of cases no plaque fissure, but only endothelial erosion can be identified under the thrombus, and *c)* occasionally no thrombus can be found.[95,97] Of note, small plaque fissures with intraintimal platelet thrombi can be found in about 10% of individuals dying of non cardiac causes and in about 20% of individuals with hypercholesterolemia, hypertension and diabetes.[95,98,99] Compared to stable angina, additional distinctive features observed in the culprit atherosclerotic plaque in unstable angina are represented by: *a)* increased concentration of inflammatory cells including activated T lymphocytes, macrophages and mast cells; *b)* increased cellular hyperplasia; *c)* increased endothelin-1 immunoreactivity, and *d)* contraction bands in the surrounding smooth muscle.[98,100-109]

Coronary spasm due to smooth muscle hyperreactivity is the predominant cause of myocardial infarction in patients with a history of vasospastic angina, although this event is rare.[110,111] However, coronary vasoconstriction and thrombosis are deeply interrelated. On the one hand occlusive coronary spasm and distal blood stagnation are known to cause a transient several fold increase of fibrinopeptide A in systemic blood.[112-113] On the other serotonin, a substance released by activated platelets, is known to produce occlusive spasm in patients with variant angina and ischemia due to distal vessel constriction in patients with chronic stable angina.[114] This vicious circle, probably mediated by serotonin, thromboxane A_2, thrombin and endothelin may have an important role in the setting of unstable angina where unstable coronary plaques frequently showing a preserved smooth muscle are in contact with activated platelets. Furthermore, several findings sustain the possibility of smooth muscle hyperreactivity in unstable angina. Indeed, unstable plaques appear to be more reactive to the stimuli of exercise and cold pressor test than stable plaques, in particular in the presence of an elevation of systemic markers of inflammation.[115-119]

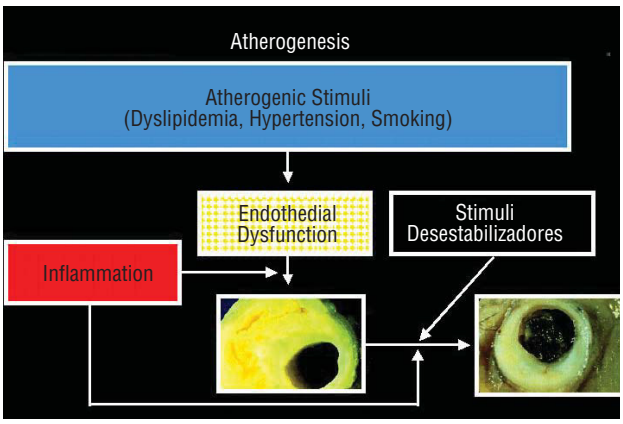

Fig. 1. Role of inflammation in atherogenesis and in the transition from stable to unstable coronary syndromes.

INFLAMMATION IN ACUTE CORONARY SYNDROMES

Evidence of Inflammation

A few years ago the occasional observation of red streaks along the course of main coronary trunks at the time of bypass surgery in unstable patients[106] and the observation of inflammatory cells infiltrated at the site of plaques and in perivascular nerves[105,106] raised the intriguing possibility that inflammation contributes to the syndrome by stimulating or enhancing local hemostatic and vasoconstrictor responses.

These post-mortem observations were subsequently confirmed by a series of clinical studies showing a systemic activation of inflammatory cells. Dinerman et al found a systemic increase in blood levels of neutrophil elastase[120] and Biasucci et al found a reduction of intracellular neutrophil peroxidation, both inducers of neutrophil activation, in patients with unstable angina or acute myocardial infarction compared to those in patients with chronic stable angina.[121] Mazzone et al found increased expression of the adhesion molecule CD11b/18 on the surface of monocytes and granulocytes sampled from the coronary sinus in patients with stable angina compared to that observed in patients

with stable angina;[122] in contrast CD11b/18 expression in aortic samples was similar in the 2 groups of patients thus suggesting transcardiac monocyte and granulocyte activation in unstable angina. Neri Serneri et al showed that human monocytes cocultured with lymphocytes from patients with unstable angina exhibited a greater procoagulant activity compared to that of monocytes cocultured with lymphocytes of patients with stable angina or controls, thus suggesting lymphocyte activation in unstable angina.[123] Berk et al found increased blood levels of CRP in patients with unstable angina compared to those with stable angina.[124] Of note, CRP is the prototypic acute phase reactant and is synthesized by the liver following stimulation by IL-6 which is mainly produced by activated monocytes; blood levels of CRP start increasing about 6 hours after the hepatic stimulation.[125] More importantly, Liuzzo et al found increased blood levels of CRP in patients with MI admitted within 6 hours of symptom onset and in patients with unstable angina and low troponin levels, in whom raised CRP levels could not be secondary to myocardial necrosis.[17] This seminal study strongly suggested for the first time that a sudden activation of inflammatory cells may play a primary role in the pathogenesis of acute coronary syndromes.

Data from our group confirmed that the inflammatory outburst associated with ACS is not an epiphenomenon, but rather a primary pathogenetic component of the syndrome. In fact, inflammation is not attributable to myocardial cell necrosis,[17] nor is it related to the severity of atherosclerosis, since there is no correlation between the degree of atherosclerosis and the acute phase response in patients with chronic stable angina or peripheral vascular disease.[126] It cannot be attributed to episodic activation of the haemostatic system since the systemic elevation of markers of thrombin production (thombin-anti-thrombin complex and prothrombin fragment 1+2) is not followed by further elevation of acute phase proteins;[127] nor it can be attributed to ischemia reperfusion injury since circulating neutrophils are not activated and CRP levels are not raised in patients with variant angina despite a significantly larger number of ischemic episodes.[128] Finally, it is worth noting that inflammation is not related to plaque rupture as no increase of IL-6 or of CRP is observed in stable patients with low baseline values of CRP undergoing balloon angioplasty, an iatrogenic cause of plaque disruption.[129]

Consequences of Plaque Inflammation

Regardless of its causes, the inflammatory outburst associated with acute coronary syndromes is the expression of activated inflammatory cells some of which are likely to be located in the culprit atherosclerotic plaque where they can determine severe detrimental effects through a variety of different mechanisms.

Endothelial Activation

The cytokines secreted by activated inflammatory cells have the potential to activate the endothelium transforming its antiadhesive and anticoagulant properties into adhesive and procoagulant properties.[1-4] Indeed, endothelial cells stimulated by IL-1, TNF or endotoxin express adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and E-selectin on their surface and secrete soluble chemoattractants such as monocyte chemoattractant protein-1 (MCP-1), monocyte colony stimulating factor (M-CSF) and IL-8.[1-4] Of note, in activated endothelial cells different adhesion molecules and chemoattractants are expressed almost simultaneously, thus suggesting a concerted activation of different genes probably, related, at least partially, to the activation of the nuclear factor κB (NF-κB)[130]. The latter was initially described in lymphocytes where it controls the activation of genes which encode for the κ chains of immunoglobulins. It consists of a family of dimeric transcription factors linked to an inhibitory protein (I-κB). The phosphorylation of I-κB results in the translocation of active subunits in the nucleus where they link to specific sequences in the promoter regions of different genes thus activating mRNA transcription.[130-132] Sequences able to link NF-κB elements have been found in several human genes, including those encoding for endothelial adhesion molecules. Thus the NF-κB system might mediate cytokine-induced endothelial synthesis of adhesion molecules and of soluble chemoattractants following endothelial activation.[130-132]

The vascular endothelium actively contributes to a dynamic balance between antithrombotic and prothrombotic activities.[68,69] Normally, endothelial cells act to prevent coagulation, but incubation with cytokines such as IL-1 and TNF-α results in an increase of procoagulant activity, which peaks at 4 hours and returns to baseline within 24 hours, probably mediated by tissue factor expression.[133] The procoagulant effects of IL-1 and TNF-α appear to be cumulative as incubation with both cytokines results in greater development of procoagulant activity than incubation with either mediator alone, even at their apparent maximal doses.[133] Of note, IL-6 increases platelet reactivity which may potentiate the procoagulant effects due to IL-1 and TNF-mediated endothelial activation.[134]

Alterations of Extracellular Matrix Metabolism

A dense, fibrous extra cellular matrix (formerly called connective tissue) is the main component of the fibrous cap of atherosclerotic plaques.[135,136] The principal constituents of this extra cellular matrix are types I

and III collagen (a triple helical coil derived from specific procollagen precursors), elastin and proteoglycans. IFN-γ elaborated by activated T reduces collagen synthesis by causing smooth muscle cell apoptosis and by specifically inhibiting collagen synthesis in smooth muscle cells.[135,136] Furthermore, lipid laden macrophages stimulated by a variety of cytokines such as INF-γ, M-CSF, MCP-1 and IL-1 release matrix metalloproteinase, such as collagenase and stromelysin, thus enhancing intercellular matrix degradation. Collagenase, stromelysin and gelatinase B can also be expressed by other cells contained in the atherosclerotic plaque such as endothelial and smooth muscle cells, following their activation by cytokines.[135,136] Finally, cytokines do not appear to affect the synthesis of tissue inhibitors of matrix metalloproteinases.[137]

In summary, plaque inflammation has the potential to enhance plaque fissuring by reducing the concentration of proteins contained in extra cellular matrix.

Hyperreactivity of Smooth Muscle Cells

Zeiher et al have demonstrated greater endothelin-1 immunoreactivity in unstable coronary plaques compared to that found in stable plaques obtained by directional atherectomy.[138] This observation may provides a clue to the mechanisms of segmental coronary hyperreactivity frequently observed in patients with unstable angina, in particular in the presence of raised CRP levels.[119] Indeed, not only is endothelin-1 a potent vasoconstrictor itself, but it also potentiates the effects of other vasoconstrictor stimuli such as catecholamines, serotonin, and angiotensin II.[139] Interestingly, endothelin is not only produced by endothelial cells but also by human macrophages and polymorphonuclear leukocytes stimulated by lipopolysaccharides. Further evidence that activated inflammatory cells can cause smooth muscle hyperreactivity is supported by the observation in a porcine model that wrapping of a proximal coronary segment with cotton mesh absorbing sepharose beads with recombinant human IL-β determines local smooth muscle hyperreactivity to serotonine and histamine within a few weeks.[140] These functional changes are prevented by simultaneous treatment with neutralizing antibodies to IL-1β or PDGF, thus suggesting that PDGF may play an important role in mediating the vasospastic response induced by IL-1β.

Causes of Inflammation

An increase of IL-6 and of CRP following coronary angioplasty or following the weak inflammatory stimulus of coronary angiography is observed in unstable patients with elevated baseline CRP levels.[129] Accordingly, peripheral monocytes from unstable patients with elevated CRP levels (>0.3 mg/dL) hyperrespond in vitro to the stimulus of lipopolysaccharide compared to monocytes from unstable patients with low CRP levels (<0.3 mg/dL), and also from stable angina patients and healthy controls (Figure 2).[141] Furthermore, in patients with acute MI the acute phase protein response to necrosis was found to be independent from infarct size, but predicted by baseline CRP levels; in this study elevated baseline CRP levels were found in 85% of myocardial infarction preceded by unstable angina.[93] Taken together, these findings suggest that hyperreactivity of inflammatory cells to subliminal inflammatory stimuli may contribute to cause coronary instability. In line with this hypothesis, an unusual subset of T cells expressing the $CD4^+CD28$ null phenotype has been identified in patients with an increased inflammatory state.[142] These unusual T cells are committed to the production of IFN-δ. The chronic up-regulation of IFN-γ in unstable angina patients could lead to subsequent activation of monocytes/macrophages in the circulation as well as in tissue lesions δ. The finding that CD28 null T cells have cytolytic capability suggests that immune reactions in individuals with such T cells are deviated towards a high risk for tissue damage. Environmental as well as genetic mechanisms could underlie the perturbation of the T cell repertoire. In particular, since the defect in CD28 cell surface expression may result from chronic exposure to antigen, the expansion of $CD4^+CD28$null T cells may reflect a persistent immune response to microorganisms or autoantigens contained in atherosclerotic plaques.[142,143]

It should be emphasized that inflammation associated with ACS is widespread and not restricted to the culprit stenosis. Accordingly, previous studies showed that ACS are associated with multiple coronary thrombosis at post-mortem examination, with microvascular impairment in remote regions and with enhanced short-term progression of non culprit stenoses.[95] Furthermore, Goldstein et al found that two fifths of patients with acute MI harbour multiple complex coronary plaques, which are associated with adverse clinical outcomes.[144] More recently, in a post-mortem study Spagnoli et al, using a novel technique for the quantitative assessment of cellular components of epicardial coronary arteries, found diffuse inflammatory cell activation both in infarct-related and in non-infarct related arteries in patients with acute MI but not in patients with old MI.[145] Finally, Buffon et al found widespread activation of neutrophils across the coronary vascular bed in patients with unstable angina, regardless of the location of the culprit stenosis.[146] In particular, the neutrophil myeloperoxidase content in blood samples taken from the great cardiac vein, which selectively drains blood from the left but not the right coronary artery, was significantly decreased in patients with unstable angina, independently of the site (left or right

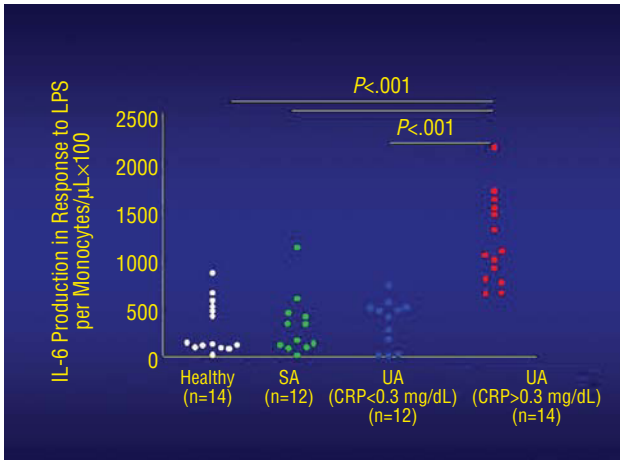

Fig. 2. Interleukin-6 (IL-6) production from monocytes following in vitro stimuli with lipopolysaccharide (LPS) in patients with unstable angina (UA) having high (>0.3 mg/dL) C-reactive protein (CRP) levels, UA patients with low (<0.3 mg/dL) CRP levels, stable angina (SA) patients and healthy controls.

coronary artery) of stenosis, but not in patients with stable angina and multiple stenoses, patients with variant angina and recurrent ischemia, or controls (Figure 3). Taken together, these pathological, angiographic, and clinical observations strongly challenge the concept of a single vulnerable plaque in unstable coronary syndromes and support the concept that plaque instability is not merely a local vascular accident but probably reflects more generalized pathophysiological processes with the potential to destabilize atherosclerotic plaques throughout the coronary tree.

The triggers of the widespread coronary inflammation associated with ACS are still unknown. Caligiuri et al found that the antigen receptor repertoire of the activated T cells was skewed in 57% of patients with unstable angina versus 23% of patients stable ischemic heart disease, supporting the hypothesis that an antigen-driven immune response may play a role in the pathogenesis of coronary instability.[147] The recent observation by Biasucci et al of seropositivity to *Chlamydia pneumoniae* heat shock protein 60 in 98% of patients with ACS, 20% of patients with stable angina and in 0% of controls suggest that *Chlamydia pneumoniae* infection resulting in expression of heat shock protein 60 might be a potential trigger, perhaps through antigenic mimicry (Figure 4).[148]

PROGNOSTIC IMPLICATIONS

In patients with ACS raised levels of CRP are associated with a worse prognosis, as initially shown by Liuzzo et al.[17] Similarly, Toss et al in an analysis of the FRISC (Fragmin In unStable Coronary artery diseases) study found that elevated levels of CRP (>10 mg/L) were associated with 8% rate of death and non-fatal MI at 150 days in unstable angina and non-

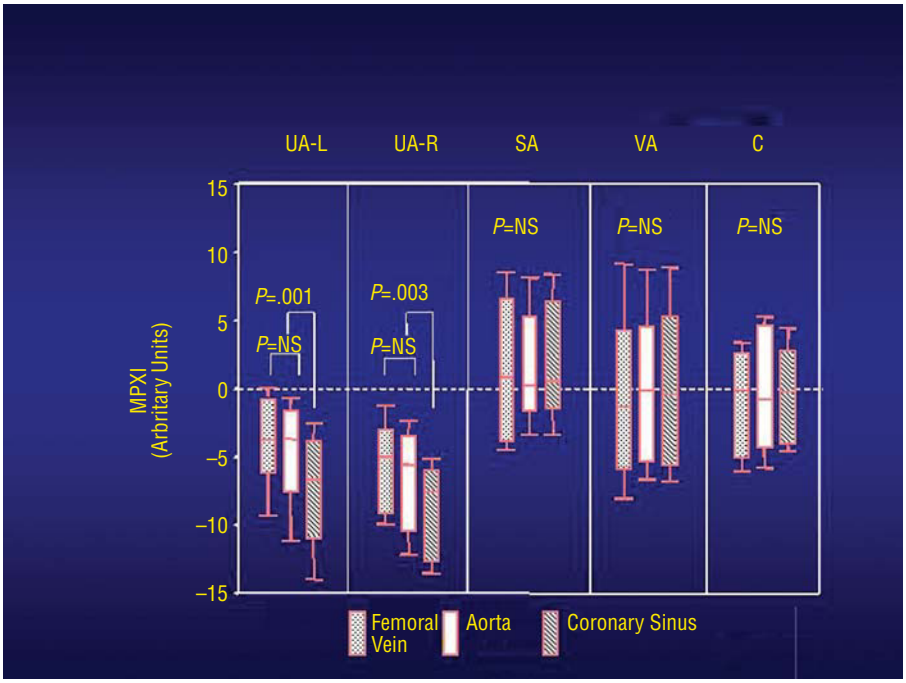

Fig. 3. Neutrophil activation, expressed as changes in myeloperoxidase (MPXI) content, drawn from the great cardiac vein (coronary sinus), aorta and femoral artery in unstable angina (UA) patients with both left (UA-L) and right (UA-R) coronary artery disease, patients with stable angina (SA), patients with variant angina (VA), and controls (C).

q wave MI patients versus 2% in patients with CRP<2 mg/L.[22] These data were confirmed in an extended follow-up at 2 years. Accordingly, Ferreiros et al have reported a follow-up study of patients with unstable angina and non-q wave MI and confirmed that elevated levels of CRP (>15 mg/L) are associated with an elevated risk of coronary events (refractory angina, death and MI) at 90 days.[23] Ridker et al also in the CARE study reported that, among post-MI patients, CRP levels on the highest quintile were associated with recurrence of events (RR, 2.8).[24] Persistence of raised CRP levels at discharge appears to be associated to a even worse prognosis. Biasucci et al found an OR of 8.7 for new unstable ischemic events during a 1-year follow-up for patients with CRP levels >3 mg/L at discharge compared with patients with CRP levels <3 mg/L which resulted statistically significant at the multivariate analysis.[18]

Troponins (T and I) represent a sensitive marker of myocardial ischemic damage, and become detectable soon after minor myocardial injury. Troponins have been proven to be extremely helpful in short and mid-term risk stratification of patients with unstable angina and non-Q wave MI[149-151] raising the question whether the prognostic value of markers of inflammation, such as CRP, is incremental to that of markers of myonecrosis. The first studies to address the issue of the incremental value of CRP on the top of troponins were published in 1998. Morrow et al. in a substudy of the TIMI 11A showed that CRP and troponin T were cumulative in UA and non-q wave MI;[25] in particular low CRP levels and negative levels of troponin T were associated with a less than 1% risk of death at 14 days versus 9% for high CRP (15 mg/L) and early positivity of bed-side troponin T. Rebuzzi et al studied 102 points with UA; confirming that the seronegativity of both markers (troponin T and >CRP) was associated with very low risk of MI (less than 2% at 3 month) and that CRP is useful for risk stratification of patients with negative troponin T, 15% of which, all with elevated CRP, had a MI at 3 months.[152] These observations were then confirmed in several other studies[153] and in particular in the FRISC study.[154]

Notably, troponins appear be more useful than CRP in predicting short term prognosis since they generally indicate the presence of complex thrombotic coronary atherosclerotic lesions associated with a high risk of early recurrences. Conversely, CRP is a marker of underlying ongoing destibilizing stimuli and therefore might represent a better marker of longer term prognosis.

What about the impact of prognostic stratification based on troponins and CRP on patient management? In a subgroup analysis of the FRISC and the TMI 11B studies, troponin T and troponin I, respectively, were able to identify patients who benefited from antithrombotic protection with low-molecular-weight heparin.[155,156] Similarly, platelet glycoprotein (GP) IIb/IIIa inhibitor administration and an invasive strategy have been shown to be beneficial in unstable patients with elevated troponin levels but not in unstable patients with normal troponin levels.[157-160] Conversely, the increased risk associated to raised levels of CRP is not abated by current treatments including potent antithrombotic regimens and an invasive strategy.[161] Thus the stage appears to be set for the search for new treatments able to efficiently counteract the increased risk conferred by the inflammatory outburst associated to ACS.

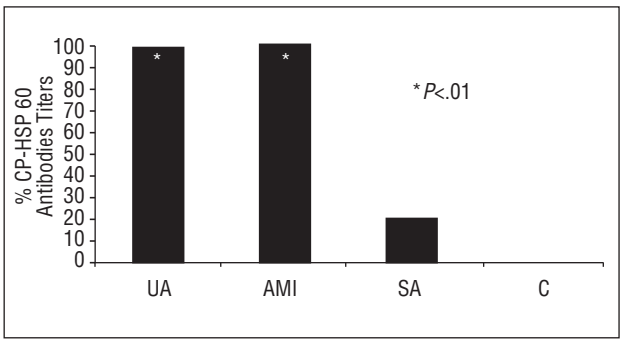

Fig. 4. Seropositivity to *Chlamydia pneumoniae* heat shock protein 60 (CP-HSP 60) in patients with unstable angina (UA), acute myocardial infarction (AMI), stable angina (SA) and healthy controls (C).

INFLAMMATION ASSOCIATED TO ACUTE CORONARY SYNDROMES AS A THERAPEUTIC TARGET

The ideal treatment of patients with ACS and systemic evidence of inflammation should target the triggers of inflammation. These triggers, however, are still elusive. Alternatively, the increased risk conferred by hyperreactivity of inflammatory cells observed in this setting might be counteracted by non specific anti-inflammatory drugs.

In the past few years several studies have shown that statins exhibit previously unsuspected anti-inflammatory effects including reduction of leucocyte adhesion and antagonism of macrophage activation.[162] In recent clinical studies statin therapy has been shown to lower CRP levels, independently of lipid lowering.[24] Post-hoc analysis have suggested benefits of statin therapy among patients with raised CRP levels, both in post-MI patients or in asymptomatic subjects.[24] To date, only the MIRACL study prospectively demonstrated a significant reduction in the recurrence of coronary instability of in-patients with ACS randomized to high dose atorvastatin treat-

ment compared to placebo during a 16-week follow-up.[163]

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may have important anti-inflammatory effects.[164] In fact, angiotensin II besides mediating vasoconstriction, stimulates cytokine, chemokine, MMP and growth factor production in endothelial and smooth muscle cells.[164] An early study suggests, furthermore, that irbesartan markedly reduces CRP levels. Controlled randomized trials are warranted to establish whether these anti-inflammatory effects are beneficial in patients with ACS and raised CRP levels.

Steroids are powerful anti-inflammatory drugs. Yet, in a randomized placebo-control study they failed to improve the outcome of patients with non ST segment elevation ACS.[165] The short duration of treatment (2 days), however, does not allow firm conclusions to be drawn. Interestingly, in the IMPRESS study patients with elevated CRP levels undergoing coronary interventions by means of coronary stent implantation were prospectively randomized to receive oral steroids for 45 days at immunosuppressive doses or placebo.[166] Steroid treatment resulted in a significant reduction in clinical event rate at 1 year from about 35% to about 5%.

Inhibitors of the cyclo-oxygenase (COX)-2 isoform are potent anti-inflammatory drugs, and might be useful in high-risk unstable patients with persistent evidence of systemic inflammation.[167] The safety and effectiveness of celecoxib in a small group of patients with refractory unstable angina not suitable for revascularization has been recently reported.[168] In this study one week treatment with celecoxib was associated with symptomatic improvement, with reduction of CRP levels and of IL-6 production following lipopolysaccharide challenge of monocytes *in vitro*. Larger studies are warranted to better assess the impact of COX-2 inhibitors on prognosis in patients with ACS.

Peroxisome proliferator-activated receptors (PPARs) present attractive anti-inflammatory effects.[169] PPARs are transcription factors belonging to the superfamily of nuclear receptors which regulate lipid and lipoprotein metabolism, glucose homeostasis and hemostasis. In particular, PPARs interfere with the NF-κB pathway, thus modulating the expression of various target genes.[169] Fibrates, a class of drugs used in the treatment of dyslipidemia, are synthetic ligands for PPAR-α whereas the insulin-sensitizing agents, such as glitazones, are high affinity ligands for PPAR-κ.[169] These drugs, in addition to their metabolic effects, have also been shown to exhibit anti-inflammatory and antithrombotic properties. Of note, administration of fenofibrate to patients with dyslipidemia resulted in decreased plasma concentrations of IL-6 and TNF-α, 2 cytokines inducing hepatic acute phase protein expression.[170] Glitazones used to treat patients with type 2 diabetes mellitus were found to lower serum levels of inflammatory biomarkers of arteriosclerosis such as IL-6, CRP and CD40L.[171-173] Controlled randomized trials with PPAR agonists in patients with ACS are warranted.

Central signaling hubs in inflammation such as NF-κB also have been suggested as a potential therapeutic target. Yet, in a recent report designed to investigate the role of NF-κB activation on atherogenesis in LDL receptor deficient mice, a macrophage-restricted deletion of IκB kinase 2 (essential for NF-κB activation by proinflammatory signals) resulted in more severe atherosclerosis.[174]

CONCLUSIONS

Systemic evidence of inflammation, probably an antigen-driven immune response, is present in about two thirds of patients with ACS. In this subset of patients the activation of inflammatory cells in the culprit stenosis is likely to play a key role in determining coronary thrombosis and vasoconstriction responsible for patient symptoms. Notably, inflammation is not limited to the culprit stenosis but it is widespread in the coronary circulation. The causes of coronary thrombosis in unstable patients with ACS who do not exhibit systemic evidence of inflammation are unknown.

Coronary instability associated with raised levels of CRP, a non specific marker of inflammation, is characterized by a worse outcome. In patients with ACS the prognostic value of CRP and troponins is incremental. Current treatments, however, diminish the increased risk conferred by raised levels of troponins, but not the increased risk conferred by raised levels of CRP. New treatments which target the triggers of inflammation or modulate the detrimental component of the inflammatory response are urgently required to further improve the outcome of this complex syndrome.

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