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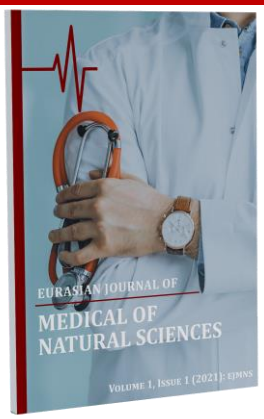


# THE ROLE OF INFLAMMATORY MEDIATORS IN THE ETIOLOGY AND PATHOGENESIS OF ISCHEMIC HEART DISEASE

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**ABSTRACT**

*Inflammation plays an important role in several stages of the cardiovascular continuum. In recent decades a plethora of studies have provided new data highlighting the role of inflammation in atherogenesis and atherothrombosis in two-way interactions with various cardiovascular risk factors and further influencing these dynamic processes. The concept of targeting residual inflammatory risk among individuals with ischemic heart disease (IHD) is therefore gaining increasing attention. In the present article, we aim to present a pragmatic overview of the complex interplay between inflammation and IHD, and to critically appraise the current evidence on this issue while presenting future perspectives on this topic of pivotal contemporary interest.*

Inflammation and cardiovascular disease: a brief overview of pathophysiological mechanisms. The myriad pathways by which inflammation can influence the atherosclerotic process are highly complex and dynamic, involving both local and systemic mechanisms. These mechanisms can be influenced by conditions such as autoimmune diseases, infections, and changes in host microbiota, but also by ambient pollution, tobacco use, medications and other external factors. Moreover, there is evidence that this interplay is modulated by the genetic background. Interestingly, illustrating the potential importance of different contexts, several studies have reported an association between infectious agents and atherosclerosis, in diverse backgrounds ranging from periodontitis to Chlamydia pneumoniae infection. Importantly, while the direct effect of single pathogenic microorganisms on the atherosclerotic plaque itself does not appear to underlie this relationship, several pathways related to chronic inflammatory stimuli have been postulated as potentially involved in this association[1]. Although trials involving anti-infectious agents such as macrolides have not shown a beneficial effect in terms of CV events, they have nonetheless provided additional insights into this complex interaction.

As mentioned, different stimuli can lead to the activation of various cell types such as lymphocytes and mast cells, leading

to expression of pro inflammatory cytokines, which in turn further modulate the activity of monocytes which migrate from the bloodstream to the vessel wall, as well as of other cell types. Notably, flow status and associated shear stress dynamics appear to play a central role in this interaction, with studies showing that specific patterns associated with atherosclerosis-prone segments can lead to differential expression of adhesion molecules by endothelial cells. As leukocytes migrate, the leukocytic infiltrate at the atheromatous plaque site can produce molecules such as proteases, procoagulant factors and inflammatory cytokines, further modulating thrombus formation and destabilization of the lesion. Among the most important cytokines involved, a delicate balance between anti-inflammatory (such as interleukin [IL]-10) and proinflammatory (such as IL-18 and IL-1 and, downstream, IL-6) signaling has a crucial role. In this balance, the NLR family pyrin domain containing 3 (NLRP3) inflammasome, a macromolecular protein complex which forms part of the innate immune system, has gained increasing prominence[2]. NLRP3 can be activated in response to different stimuli (particularly pathogen-associated or damage-associated molecular patterns, some of which can be induced due to cholesterol accumulation, hypoxia or dysregulation in autophagy), and lead to a proinflammatory cytokine shift and cell death (via pyroptosis, a form of programmed cell death via specialized caspases).

Another issue to be considered is the production of autoantibodies (including cardiac autoantibodies). These may be related to background autoimmunity (as in the case of systemic lupus erythematosus) and further amplify the immune response, but can also be found in individuals with CVD as well as in the general population, thus further illustrating the overlap between mechanisms. In addition, data support the notion that there are changes in the leukocyte profile in CVD. Although the full scope of these findings remains to be fully ascertained, a proinflammatory imbalance as expressed by changes in the neutrophil-to-lymphocyte ratio, suggesting a shift towards increased inflammatory mediators via neutrophils and a reduction in anti-inflammatory signaling via lymphocytes, has been proposed as among the mechanisms underlying the association between changes in blood cell profiles and CVD. Furthermore, in parallel with the intense crosstalk between cell types (promoted by a proinflammatory imbalance in the cytokine milieu), oxidative stress may also have an important role, affecting different cellular components and further promoting the evolving atherogenic process. Mitochondrial dysfunction can also lead to activation of the NLRP3 inflammasome by way of reactive oxygen species, while altered mitochondrial homeostasis can perpetuate this maladaptation.

**Inflammation and atherothrombosisInflammation as a cardiovascular risk factor**. Given the evidence supporting an association between inflammation and CVD, the concept that inflammation could be considered a risk marker or risk factor has continued to evolve in recent years. C-reactive protein (CRP) has provided important evidence on this issue. This protein, mainly synthesized in hepatocytes

and whose mRNA transcription is influenced by IL-6 and IL-1β, is released in response to a plethora of stimuli, such as infections and trauma, forming part of a non-specific innate defense mechanism. The sole determinant of its plasma concentration is its rate of synthesis, making it an interesting biomarker for assessing the intensity of the stimuli which lead to its production. Even so, CRP is a downstream marker that is probably not directly related to the atherogenic process itself[3].

Notwithstanding, high-sensitivity CRP (hs-CRP) assays, which are able to assess lower levels of CRP (such as those associated with low-grade inflammation), have emerged as important ancillary tools for understanding the association between inflammation and ischemic events. Several studies have shown that hs-CRP levels can predict CV events, both in the general population and in individuals with previous CVD. Various reports have shown that hs-CRP level can discriminate CV risk independently of lipid parameters, highlighting its potential role as a risk marker.

While data have shown an association between several CV risk factors and inflammation, recent studies have progressively refined this relationship. The seminal JUPITER trial, which assessed the effect of rosuvastatin on individuals without CVD who had LDL cholesterol (LDL-C) <130 mg/dl and elevated hs-CRP (≥2 mg/l), provided important insights[4]. In this study, rosuvastatin was associated with significant reductions in the primary composite endpoint, while also reducing all-cause death. Importantly, rosuvastatin was associated with significant reductions in both LDL-C and hs-CRP. Since this study, trials assessing proprotein convertase subtilisin/kexin type 9 inhibitors, which can reduce LDL-C to levels below those achieved with statin therapy and which do not substantially reduce hs-CRP levels, showed important reductions in CV events. At the other end of the spectrum, in the landmark CANTOS trial, canakinumab, which lowered hs-CRP without affecting LDL-C levels, reduced CV event rates, providing further arguments for the potential of targeting inflammation in CV prevention strategies. Current data thus reinforce the complementarity between inflammation and traditional CV risk factors in atherosclerosis, although historically a putative dichotomy between these components had at times been perceived[5].

**Inflammation in patients with ischemic heart disease**. As discussed above, there is ample evidence supporting the role of inflammation at different stages of atherosclerosis, interacting with other factors to promote damage signaling and thus modulate this process. It should be borne in mind that inflammatory stimuli can be associated with several CV risk factors, leading to atherogenesis and thus IHD. Another factor that further influences disease expression is the intense interplay between inflammation and hemostasis, which can lead to a prothrombotic state.

Several reports suggest that after an acute coronary event, inflammation may provide a link to a higher residual risk. Although the beneficial impact of optimized standard secondary prevention strategies is undisputed, the significant risk of further events in this patient population has led to marked interest in strategies to reduce this residual risk. Given this background and the wealth of data supporting the increased risk

of CV events among IHD patients with elevated hs-CRP, the putative role of residual inflammatory risk has increasingly attracted attention. While the potential of inflammatory modulation in CV risk has been hypothesized for over twenty years, data exploring the role of specific blocking of inflammatory pathways in IHD are still scarce[6]. Insights from randomized controlled trials published in recent years have highlighted the link between inflammation and residual risk in IHD, providing novel paradigms in risk mitigation.

**Cardiac Injury Activates Inflammatory Pathways.** Cardiac acute local inflammation is a process with a vast array of causes; these vary from infectious, toxins, or myocardial infarction. Infectious inflammatory myocarditis may be associated with viruses, bacteria, fungal entities, or parasites. From these, viral myocarditis is of particular interest due to its progression to dilated cardiomyopathy (DCM) and HF . From an inflammatory standpoint, most viral infections can be cleared without sequelae. However, some infections are associated with cardiomyocyte lysis after entering these cells and releasing self-antigens. Cardiomyocytes have a higher rate of being infected than fibroblasts, although the latter have higher replication rates . After infection, the host mounts an inflammatory response through the production of several pro-inflammatory cytokines, such as IL-1α, IL-6, TNF-α, IFN-γ, and the activation of monocytes and NK cells, which induce apoptosis in infected cells[7]. As mentioned previously, viral myocarditis is linked to DCM, and although not well understood, in any cardiac inflammatory setting, there is a risk to develop chronicity, as has been recently shown by Groot and Hilde, from non-obstructive cardiovascular disease to ischemic HF . The interplay of increased cytokines also skews T cells between Th1/Th2 and Th17/Treg responses , each with specific inflammatory functions, yet all associated with chronic inflammation when skewed.

During an ischemic event, the neutrophils are the first cells to arrive and infiltrate the tissue, and it has been demonstrated that the basal levels can predict the progression to ischemic HF. Once in the myocardium, influenced by the release of inflammatory cytokines, neutrophils activate and release a series of inflammatory mediators such as high levels of reactive oxygen species (ROS), IL-1β, myeloperoxidase, and proteases, which increase local tissue injury . Of note, the increase in neutrophil counts and/or its ratios, such as neutrophil: lymphocytes and neutrophil: platelet ratio , have demonstrated to have clinical relevance in stratifying a patient's severity. This cytokine-mediated inflammation contributes to inflammatory loops and induces sub-acute and chronic inflammation . Persistence of this inflammatory response causes additional secondary damage to the nearby tissue. There is also enough evidence of the effect of inflammation influencing the dysfunctional contractile state in HF, for example, by TNF-α . Finally, some specific neutrophils can induce polarization of monocytes to a reparative phenotype, inducing a pathologic production of fibrosis.

The inflammatory response to the pathogens, infected cells, and damaged cells/tissues, which release DNA and ROS , elicits the activation of pattern recognition receptors (PRR), such as toll-like receptors

(TLRs) and nucleotide-binding and oligomerization domain- (NOD-) like receptors (NLRs) as NLRP3 (NOD-, LRR-) associated with the inflammasome. NLRP3 inflammasome activation results in IL-1β and IL-18 cytokine production, both related to cardiac dysfunction, reduced left ventricular contractility, worsening, and increased mortality . On the one hand, IL-1β promotes contractile dysfunction and secondary cytokine-induced damage[8].

The risk of chronic inflammation to become systemic is also closely related to the induction of an autoimmune scenario, where the initial damage of the tissue is associated with the presentation of an antigen or a similar self-antigen, thereby initiating the damage modulated by CD4 cells and promoted by CD8 cytotoxic cells by its perforin, granzyme, and FAS-mediated apoptosis induction mechanism. Alongside the effects of T cells, B cells have an active and critical role in the development of HF remodeling and dysfunction , either by modulating inflammatory cell recruitment or by increasing the inflammatory response through the production of autoantibodies and fibrosis[9]. Moreover, interfering T cell co-stimulation by antigen presenting cell (dendritic cell, macrophages, and B cells) attenuates heart dysfunction mediated by IL-10-producing B cells.

Conclusion. Recent decades have provided extensive and mounting evidence concerning the pivotal interplay between inflammation and IHD, reinforcing the concept of inflammation not only as a risk marker but also as a risk factor for the development and progression of atherosclerotic disease[10]. Although additional assessment is needed to fully ascertain the full scope of this intervention, particularly in terms of patient selection and optimal therapeutic tailoring in light of contemporary CV prevention strategies, these findings have the potential to challenge the current status quo of ischemic risk reduction.

As the holistic approach to IHD continues to be further refined, based on a robust translational background and benefiting from the input of greatly improved ancillary diagnostic methods and an expanding therapeutic armamentarium, investigation of the specific role of inflammatory modulation is set to take center stage, in the current age of precision-based medicine.

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