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STATE-OF-THE-ART PAPERS

Anti-Inflammatory Strategies for Ventricular Remodeling Following ST-Segment Elevation Acute Myocardial Infarction

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Acute myocardial infarction (AMI) leads to molecular, structural, geometric, and functional changes in the heart in a process known as ventricular remodeling. An intense organized inflammatory response is triggered after myocardial ischemia and necrosis and involves all components of the innate immunity, affecting both cardiomyocytes and noncardiomyocyte cells. Inflammation is triggered by tissue injury; it mediates wound healing and scar formation and affects ventricular remodeling. Many therapeutic attempts aimed at reducing inflammation in AMI during the past 3 decades presented issues of impaired healing or increased risk of cardiac rupture or failed to show any additional benefit in addition to standard therapies. More recent strategies aimed at selectively blocking one of the key factors upstream rather than globally suppressing the response downstream have shown some promising results in pilot trials. We herein review the pathophysiological mechanisms of inflammation and ventricular remodeling after AMI and the results of clinical trials with anti-inflammatory strategies. (J Am Coll Cardiol 2014;63:1593–603) © 2014 by the American College of Cardiology Foundation

Acute myocardial infarction (AMI) remains a leading cause of death worldwide (1). Despite reperfusion strategies, patients with large AMI who survive the initial ischemic event are at higher risk of the development of HF in a process referred as ventricular remodeling (2). The term ventricular remodeling, first used by Pfeffer et al. (3) in 1985, refers to changes in ventricular geometry (dilation, sphericity, wall thinning) and stiffness, as well as epigenetic, molecular, and functional changes that include both cardiomyocytes and other cells of the heart, in the infarct area, and in the remote viable myocardium (4). Ventricular remodeling is a powerful prognostic factor after AMI (5) and has been identified as a target for intervention.

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Despite modern reperfusion strategies (with a goal of door-to-balloon time of <90 min) and neurohormonal blockade therapies (inhibitors of the renin-angiotensin-aldosterone system and of the adrenergic system), the incidence of HF after ST-segment elevation AMI remains unacceptably high, and there is an urgent need for novel treatments to improve post-AMI quality of life and survival. This suggests that the current therapeutic paradigm still misses one or more key pathophysiological mechanisms.

Parallel to the interest in reperfusion and neurohormonal blockade, much interest has been devoted to understanding the role of inflammation in AMI (6), leading to a large volume of experimental preclinical data and clinical observation evidence but, unfortunately, not to any clinically effective anti-inflammatory treatments for AMI.

The aim of this review is to discuss the activation of the inflammatory response and its role in post-AMI ventricular remodeling, the basis of preclinical research, the potential reasons for failure to translate, and future perspectives in the field.

Pathophysiology

The heart has limited anaerobic metabolism and depends on oxygen. During AMI, the oxygen supply is reduced and adenosine triphosphate is no longer produced, with

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Abbreviations and Acronyms

AAT = alpha$_1$-trypsin
AMI = acute myocardial infarction
COX = cyclooxygenase
CRP = C-reactive protein
CVF = cobra venom factor
HF = heart failure
IL = interleukin
IL-1R1 = interleukin 1 receptor 1
IVIG = intravenous immunoglobulin
MACE = major adverse cardiac event(s)
MMP = metalloproteinase
PCI = percutaneous coronary intervention
PI3K = phosphoinositide 3-kinase
RCT = randomized clinical trial
STEMI = ST-segment elevation myocardial infarction
TNF = tumor necrosis factor
TNFR = tumor necrosis factor receptor

impairment of the sodium-potassium (Na^+-K^+ ATPase) pump and loss in membrane integrity, leading to death (6,7).

After the initial ischemic event, an intense inflammatory response is observed, mainly characterized by infiltration with neutrophils, followed by monocytes/macrophages and lymphocytes. Infiltrating monocytes first express a proinflammatory (M1) phenotype, followed by a switch to an angiogenic and fibrotic phenotype (M2) (8,9). Infiltrating lymphocytes, although smaller in number, also play a key role in remodeling. CD4 T-helper lymphocytes shift to a Th1 phenotype, whereas regulatory T cells are necessary for resolution of inflammation (6,10). In the initial few days, the infarct starts to expand as a result of the loss of passive tension. Infarct expansion is characterized by acute ventricular dilation, infarct wall thinning (without additional necrosis), and cardiomyocyte stretching. Extracellular matrix degradation promotes cardiomyocyte slippage and scar thinning. Cardiac fibroblasts generate a noncompliant collagen scar to maintain the ventricular geometry and prevent aneurysm formation. This process is followed by maturation of the scar. Apoptosis of infiltrating neutrophils and a phenotypic switch in macrophages and lymphocytes are involved in the resolution of the inflammatory process (6,8,10).

This healing process in post-AMI ventricular remodeling can be divided into 3 partially overlapping phases (6): 1. the inflammatory phase; 2. the proliferative phase; and 3. the maturation phase. The inflammatory phase is mediated by cytokines leading to recruitment of leukocytes. Cell debris activates the inflammasome, a macromolecular structure that activates caspase-1 and the conversion of pro-interleukin (IL)-1β to mature IL-1β (11,12). The formation and activation of the inflammasome amplify tissue injury and the local and systemic inflammatory response (11,12). Leukocytes remove necrotic cells while releasing cytokines and growth factors. Neutrophils eventually undergo apoptosis, leading to a gradual disappearance of the infiltrate. In the proliferative phase, fibroblasts proliferate and synthesize collagen to form a scar.

The most effective therapeutic intervention to reduce myocardial injury is timely and effective myocardial reperfusion. The process of myocardial reperfusion, however, can itself induce further cardiomyocyte death with a phenomenon known as myocardial reperfusion injury (13).

Over time, the increased wall stress and neurohormonal activation, however, causes apoptosis of the cardiomyocytes in the nonischemic area leading to left ventricular wall thinning and chamber dilation, producing a spherical geometry with an increased left ventricular mass but decreased relative wall thickness (eccentric hypertrophy) (7). Although ventricular dilation observed during the initial phases may be beneficial in maintaining cardiac output via an increase in ventricular filling volume, these compensatory mechanisms become detrimental when sustained over time, leading to cardiac dysfunction and heart failure (Fig. 1).

Anti-Inflammatory Treatments

Several experimental studies in animals have explored treatments aimed at modulating inflammation during AMI. Only those strategies that were eventually tested in clinical studies are discussed in detail in this review.

Glucocorticoids. Glucocorticoids are potent anti-inflammatory agents that act via 3 mechanisms (14): first, binding a receptor in the cytosol that moves to the nucleus and binds as a dimer to DNA sequences called glucocorticoid-responsive elements, modifying DNA transcription; second, the cortisol-glucocorticoid receptor complex inhibits nuclear factor κB, regulating the transcription of proinflammatory mediators; and third, via membrane-associated receptors (nongenomic pathways) independent of gene expression, such as activation of endothelial nitric oxide synthase.

In experimental animal models, treatment with glucocorticoids showed conflicting results (15,16), associated with impaired healing, scar thinning, ventricular aneurysm, and increased risk of ventricular rupture (17,18). Several rather small clinical studies tested the effects of glucocorticoids in patients with AMI, showing conflicting results. A recent systematic review and meta-analysis (16 studies, n = 4,000) in AMI included registries, case-control studies, and nonrandomized and randomized clinical trials (RCTs) (19). The analysis of mortality (11 studies, n = 2,646) showed a 26% relative risk reduction with glucocorticoid therapy and no excess risk of rupture. However, there was no significant survival benefit when only RCTs or larger studies (n = >100) were included. Differences in study design, investigational agents (e.g., hydrocortisone, dexamethasone, prednisone, methylprednisone), and dosing regimens make it difficult to draw any definitive conclusions. Finally, none of the studies used a percutaneous coronary intervention (PCI) as a reperfusion strategy, and some studies were performed with no reperfusion strategy used. Overall, treatment with glucocorticoids was not harmful in this group and in some instances might be even beneficial. The impairment in infarct healing with corticosteroids is not supported by clinical trials, and it is either only seen in some subsets of patients (i.e., long-term steroid use, first AMI, transmural AMI without reperfusion)