Post-Infarction Inflammation and Left Ventricular Remodeling
– A Double-Edged Sword –

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After myocardial infarction (MI), inflammatory cells such as neutrophils, followed by monocytes and macrophages, infiltrate and phagocytose the necrotic tissues, as well as secreting a variety of inflammatory cytokines. The vulnerable myocardium, which consists of necrotic tissue and inflammatory cells, is susceptible to wall stress, resulting in infarct expansion. Subacute cardiac rupture is an extreme form of infarct expansion, whereas ventricular aneurysm is its chronic form and a trigger for subsequent left ventricular (LV) remodeling. Although post-infarction inflammation is essential for the healing process, excessive inflammation could play an important role in the development of LV remodeling. Increase in the C-reactive protein level, which reflects myocardial inflammation, is reported to be a useful predictive marker for cardiac rupture, ventricular aneurysm and LV remodeling. In addition, an increase in peripheral monocyte count is associated with a poor outcome after MI, and an animal study has demonstrated that granulocyte/macrophage-colony stimulating factor induction causes excessive macrophage infiltration in the infarcted area and worsening of LV remodeling. Recently, it was also found that dendritic cells play an important role in controlling excessive inflammation caused by monocytes/macrophages. Thus, inflammation that develops after MI is a double-edged sword, and how to control inflammation to suppress pathological remodeling is an important issue to be considered in developing new treatment for heart failure. (Circ J 2013; 77: 580–587)

Key Words: Biomarkers; Heart failure; Inflammation; Myocardial infarction; Remodeling

Left ventricular (LV) remodeling after myocardial infarction (MI) is the process of infarct expansion followed by non-infarct hypertrophy and progressive LV dilation, and is associated with adverse clinical outcomes. Defective infarct healing, as well as infarct size and wall stress, is a major determinant of infarct expansion. A well-orchestrated inflammatory response after MI leads to an appropriate infarct healing process and formation of a scar with tensile strength, preventing infarct expansion. Despite the importance of the inflammatory response and healing process in post-MI LV remodeling, the mechanisms that initiate and control these processes have not been fully elucidated. Numerous clinical and experimental studies have focused on the role of inflammation and its regulatory mechanism as a novel therapeutic target for post-infarction LV remodeling.

Increase in Body Temperature and Post-MI Complications

The 4 classical signs of inflammation are dolor, tumor, rubor and calor. It has also been recognized for a long time that body temperature increases after MI, reflecting the development of inflammation after tissue necrosis, but it was believed to be a non-specific response to tissue damage. However, an investigation into the relation between the peak body temperature during the first week and in-hospital complications since the event of MI showed that the incidence of complications of pump failure (grade of class 2 or greater according to Killip’s classification or subset II or greater according to Forrester’s classification) and ventricular aneurysm, as well as the incidence of cardiovascular events such as cardiac death, pump failure, fatal ventricular arrhythmias and cardiac rupture, increased in proportion to the body temperature increase. Although the peak creatine kinase (CK) level, an indicator of infarct size, was similar, LV end-diastolic and LV end-systolic volumes measured by left ventriculography before discharge had increased and the LV ejection fraction decreased in proportion to the body temperature increase. Increase in peripheral monocyte count is associated with a poor outcome after MI, and an animal study has demonstrated that granulocyte/macrophage-colony stimulating factor induction causes excessive macrophage infiltration in the infarcted area and worsening of LV remodeling. Recently, it was also found that dendritic cells play an important role in controlling excessive inflammation caused by monocytes/macrophages. Thus, inflammation that develops after MI is a double-edged sword, and how to control inflammation to suppress pathological remodeling is an important issue to be considered in developing new treatment for heart failure. (Circ J 2013; 77: 580–587)

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Post-MI Inflammation and Infarct Expansion

During the acute phase of MI, resident macrophages in the myocardial tissue are activated following neutrophil infiltration into the infarcted region. CD11b/18 on the surface of neutrophils plays a critical role in the activation of macrophages. This activation is mediated by the interaction of CD11b/18 with its ligands, such as mannose receptor and fibrinogen. In addition, neutrophils secrete a variety of inflammatory cytokines, including interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinases (MMPs), which contribute to the development of infarct expansion. Thus, the inflammatory response after MI is a double-edged sword, and how to control inflammation to suppress pathological remodeling is an important issue to be considered in developing new treatment for heart failure. (Circ J 2013; 77: 580–587)

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Post-Infarction Inflammation and LV Remodeling

C-reactive protein (CRP) and LV remodeling

The increase in a non-specific inflammatory marker, CRP, peaks 2–3 days after the onset of MI, and the CRP level rises further if reperfusion is not performed. It is reported that based on multivariate analyses, an extremely severe inflammatory response with serum CRP level $\geq 20$ mg/dl is an independent strong predictor of subacute cardiac rupture and ventricular aneurysm. Although the increase in CRP level may be affected by the infarct size, subacute cardiac rupture and ventricular aneurysm because of infarct expansion are more often seen in patients with a relatively larger increase in the serum CRP level compared with the peak serum CK level (Figure 2). Furthermore, a prospective study has demonstrated that the group of patients with peak CRP level above the median had a greater increase in LV volume at 2 weeks, as well as at 6 months, compared with the group of patients with peak CRP level below the median, indicating an association between inflammation and adverse LV remodeling.

In addition, a greater elevation of the CRP level was found to be a determinant of LV mural thrombus formation after MI. If there is any relation between inflammation and ventricular aneurysm formation, it may be natural that elevation of CRP serves as a predictor of mural thrombus. However, 80% or more of mural thrombi after MI are reported to form within 1 week from MI onset, but in such cases, the infarct size has been shown to be rather small. It is also recognized that ventricular aneurysm forms by infarct expansion. In addition to increased wall stress, excessive inflammatory response and disturbance of the post-infarction healing process may be involved in the development of these complications (Figure 1).

**Figure 1.** Association of post-infarction inflammation with left ventricular remodeling. Extreme infarct expansion may lead to subacute cardiac rupture, and chronic infarct expansion results in ventricular aneurysm formation and progresses to chronic heart failure combined with compensatory hypertrophy/dilatation in non-infarcted myocardium. Post-infarction inflammation plays an important role in infarct expansion. HMGB1, high mobility group box 1; IL, interleukin; CRP, C-reactive protein.
Modification of CRP Elevation by Patient Demographic Factors

Elevation of serum CRP level is known to be influenced by patient demographic factors, of which aging is an important factor. A study in patients with first anterior ST-segment elevation MI (STEMI) who underwent primary percutaneous coronary intervention (PCI) demonstrated that older patients (≥70 years old) had increased and prolonged CRP elevation after MI compared with younger patients (<70 years old) despite no significant difference in infarct size. Furthermore, among patients who were started on administration of β-blocker within 24 h from MI onset, the increase in serum CRP level was reported to be attenuated and the incidence of cardiac rupture

Figure 2. Relation between peak creatine kinase (CK) level and peak C-reactive protein (CRP) level after first myocardial infarction. The 2 values were significantly positively correlated, but patients who had a higher peak CRP level rather than peak CK level (first quadrant of graph) had more complications of subacute cardiac rupture and ventricular aneurysm, suggesting an association between CRP increase and infarct expansion.

Figure 3. Mechanism of mural thrombus formation after myocardial infarction (MI). Activation of the coagulation cascade and platelets by inflammation, as well as hemostasis, with akinetic or dyskinetic wall motion is involved in mural thrombus formation after MI.
Post-Infarction Inflammation and LV Remodeling

Post-infarction inflammation and LV remodeling were increased by 40% in experimental models, suggesting direct damage to myocardial tissue. MCP-1 expression by CRP in vascular endothelial cells and angiotensin II type I receptor expression in vascular smooth muscle cells also increased, indicating the possibility of CRP triggering inflammation and activating the RA system. CRP has a pentameric structure that dissociates into monomers upon contact with activated platelets, becoming a ligand for the Fcγ receptor on monocytes and macrophages, activating various signaling cascades and enhancing inflammation.

To examine the direct effect of CRP on LV remodeling, CRP was overexpressed in transgenic mice, and adverse LV remodeling was demonstrated. Macrophage infiltration, increased NF-κB activation and oxidative stress, and cardiac hypertrophy and myocardial fibrosis were exacerbated. In diabetic cardiomyopathy models, overexpression of CRP activated the RA system, enhanced inflammation and oxidative stress, promoted fibrosis, and aggravated LV dysfunction. Therefore, CRP is not a simple marker and may be involved in worsening pathological conditions by amplifying inflammation and promoting the RA system and oxidative stress.

**Direct Pathogenic Effect of CRP**

Originally, CRP was identified as a protein that binds to the C-polysaccharide of pneumococcus, but it is known to have a direct effect on activating complement. In autopsy cases, deposition of complement and CRP in the infarcted myocardium was reported, and deposition of complement and macrophages, as well as CRP, in myocardial biopsy samples of patients with dilated cardiomyopathy has been also reported. In addition, administration of human CRP to a rat ischemia-reperfusion (IR) model increased the deposition of complement in the myocardium and increased the size of infarction by 40%. These findings suggest the possibility that CRP directly damages myocardial tissue. Moreover, an in vitro study showed an increase in MCP-1 expression by CRP in vascular endothelial cells and an increase in angiotensin II type I receptor expression in vascular smooth muscle cells, suggesting the possibility that CRP may trigger inflammation and activate the RA system, resulting in the promotion of cardiovascular remodeling. CRP has a stable pentameric structure in blood, but it dissociates into monomers upon contact with activated platelets, becoming a ligand for the Fcγ receptor on monocytes and macrophages, activating various signaling cascades and enhancing inflammation.

To examine the direct effect of CRP on LV remodeling, transgenic mice with ubiquitous overexpression of human CRP by CAG promoter were created, and adverse LV remodeling was demonstrated. Macrophage infiltration, increased NF-κB activation and oxidative stress, and cardiac hypertrophy and myocardial fibrosis were exacerbated. In diabetic cardiomyopathy models, overexpression of CRP activated the RA system, enhanced inflammation and oxidative stress, promoted fibrosis, and aggravated LV dysfunction. Therefore, CRP is not a simple marker and may be involved in worsening pathological conditions by amplifying inflammation and promoting the RA system and oxidative stress.

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**Figure 4.** Inflammation and repair after myocardial infarction (MI) and its regulatory mechanism. Dendritic cells play a protective role against left ventricular remodeling by regulating the homeostasis of monocytes and macrophages during the transition from inflammation to repair after MI. Ly6C<sup>high</sup> mono, inflammatory monocytes; M1 Mφ, classically activated (inflammatory) macrophages; Ly6C<sup>low</sup> mono, anti-inflammatory monocytes; M2 Mφ, alternatively activated (anti-inflammatory) macrophages.
Peripheral Leukocytosis and Monocytosis After MI and Prognosis

It has long been recognized that an increase in the peripheral white blood cell (WBC) count correlates with the outcome of MI.28 A large-scale study with 153,213 patients aged 65 years or older with MI demonstrated that a higher WBC count within 24h of admission was associated with higher mortality within 30 days.29 However, leukocytosis immediately after MI is caused by the release of neutrophils pooled in blood vessels, spleen and liver, and in that case, the peripheral WBC count changes within hours. Therefore, WBC count on admission may vary depending on the time from onset to admission. On the other hand, monocytes increase in the peripheral blood and peak 2–3 days after MI. Monocytes infiltrate into the infarcted region and differentiate into macrophages, surviving for several weeks. Maekawa et al studied the association between peripheral monocytosis after MI and clinical outcomes in patients with first reperfused MI, and reported that a monocyte count ≥900/mm³ in peripheral blood was associated with a higher risk of pump failure or ventricular aneurysm formation, as well as a higher incidence of late-phase major adverse cardiac events, including hospitalization because of heart failure, reinfarction and cardiac death.30

Role of Monocytes/Macrophages in Post-MI Inflammation and Healing

The association between post-infarction monocytosis and poor long-term clinical outcome suggests that the increase in monocytes in the peripheral blood may be directly involved in myocardial damage after they infiltrate into the infarcted region. When granulocyte/macrophage-colony stimulating factor, which increases the number of peripheral monocytes and promotes the differentiation of monocytes to macrophages, was administered to a rat MI model, increased infiltration of macrophages in the infarcted region, as well as promotion of infarct expansion and exaggerated LV remodeling, were confirmed.31 Therefore, excessive inflammation via monocytes and macrophages may disturb the healing process of the myocardium after MI.

Monocytes and macrophages can be divided into several subsets according to their functions. Mouse macrophages are divided into (1) inflammatory monocytes (Ly6C<sup>hi</sup>) with high expression of CC chemokine receptor (CCR2) and low expression of the fractalkine receptor CX3CR1 (Ly6C<sup>hi</sup>/CCR2<sup>lo</sup>, CX3CR1<sup>low</sup>) and (2) anti-inflammatory monocytes (Ly6C<sup>lo</sup>) which is a smaller subset with Ly6C<sup>lo</sup>/CCR2<sup>lo</sup>/CX3CR1<sup>lo</sup>.32 After MI, expression of MCP-1, a ligand of CCR2, to the inflammatory site, such as priming of antigen-specific immune responses, induction of tolerance, and chronic inflammation.33 Group myoblast DCL in a rat MI model, and found that DCs infiltrated into the infarcted and border areas, peaking on day 7.34 In order to clarify the significance of DCs, we transplanted BM cells from transgenic mice, which had diphtheria toxin (DT) receptor and GFP incorporated downstream of the CD11c (a specific marker for DC) promoter, into irradiated recipient mice. It was confirmed that BM-derived DCs infiltrated into the infarcted myocardium after MI and DC infiltration was almost completely suppressed by administration of DT, which specifically depleted DCs transplanted from the transgenic mice. In DC-ablated mice, LV remodeling after MI was deteriorated compared with the control mice. Examination of pathologic specimens did not show a difference in infarct size, but there was wall thinning and expansion, and impaired neangiogenesis, in the infarcted myocardium compared with the control MI group. Infiltration of inflammatory monocytes (Ly6C<sup>hi</sup>) and M1 macrophages increased, whereas infiltration of anti-inflammatory monocytes (Ly6C<sup>lo</sup>) and M2 macrophages was reduced. Moreover, in the DC-ablated model, the expression of inflammatory cytokines increased while that of IL-10, which has anti-inflammatory activity, decreased and MMP-9 activity increased after MI.35 These findings suggest DC ablation resulted in enhanced inflammation and extracellular matrix degradation through activation of inflammatory monocytes and M1 macrophages and impaired post-infarction healing process through suppression of anti-inflammatory monocytes and M2 macrophages. Because DCs, macrophages, and monocytes are members of the mononuclear phagocyte system and their origins are presumed to be the same BM precursor cells, named macrophage DC progenitors.46,47 it is possible that selective DC depletion may change the subpopulations of the system. DCs may play a protective role against post-infarction LV remodeling by regulating the homeostasis of monocytes and macrophages during the transition from inflammation to repair (Figure 4).

Significance of High Mobility Group Box 1 (HMGB1) Protein as New Marker

HMGB1 is a non-histone protein known to exist in the nuclei of a variety of cells. Usually, it binds to DNA and stabilizes the nucleosome structure, but it functions as a transcriptional regulator through local distortion in the DNA structure in response to stimuli.48 HMGB1 is known to function as an inflammatory mediator when released outside the cell. It has 2 mechanisms of release: “passive release” into the blood from...
inside the cell associated with cell necrosis, and “active secretion” through the production and secretion of HMGB1 produced in inflammatory cells. HMGB1 stimulates infiltrating cells via the Toll-like receptor (TLR)-2,4 of macrophages and DCs, as well as by the receptor for advanced glycation end-products (RAGE), and activates NF-κB to promote expression of inflammatory cytokines.48-51 HMGB1 released into the blood by local tissue destruction affects the TLR and RAGE of inflammatory cells of each organ, and expands and prolongs inflammation. HMGB1 is known to be involved in conditions such as systemic inflammatory response syndrome, acute lung injury (ALI), AKI, and acute respiratory distress syndrome (ARDS).52

In a study that measured the serum HMGB1 level in STEMI or chronic stable angina (CSA) patients, the level on admission in STEMI patients was higher than that in CSA patients, peaked after 12 h and remained high 2 weeks later. With regard to in-hospital complications, the maximum serum HMGB1 level was high in patients who had pump failure, cardiac rupture or cardiac death.53 The peak serum CRP level is reached 2–3 days after MI, whereas the HMGB1 level was the highest 12 h after MI. Therefore, it is considered that HMGB1 is a biomarker that enables risk stratification earlier than does CRP.

Based on the finding from clinical studies that a rise in serum HMGB1 is associated with a poor clinical outcome, we initially hypothesized that HMGB1 suppression may mitigate inflammation after MI and improve LV remodeling, and conducted an experiment to administer anti-HMGB1 neutralizing antibody to a rat MI model for 1 week after coronary ligation. Inflammatory cytokines and HMGB1 mRNA expression, as well as macrophage infiltration in the myocardium, were suppressed by neutralizing antibody administration. However, contrary to expectation, LV remodeling worsened after MI.54 This means that inflammation is essential for the healing process after MI, despite the fact that excessive inflammation serves as a predictive marker of a poor clinical outcome. Therefore, inflammation is a double-edged sword, and this experiment suggests the possibility that HMGB1 is a prerequisite for the healing process after MI. One study has shown the possible important role of HMGB1 in the healing process; administration of HMGB1 locally into the peri-infarcted area in a mouse MI model attenuated LV remodeling and promoted differentiation of cardiac stem cells into cardiomyocytes.55 In another study in which MI was induced in transgenic mice with cardiac-specific overexpression of HMGB1, angiogenesis was promoted while LV remodeling after infarction was suppressed.56 These results indicate that HMGB1 may be an important signal, triggering cardiac regeneration and angiogenesis. On the other hand, in a recent report, intraperitoneal administration of HMGB1 in a mouse IR model promoted LV remodeling, together with an increase in the inflammatory response after MI, but administration of an HMGB1 antagonist reduced IR injury and improved LV function.56 Although the coronary artery ligation model and IR model may have different pathologic mechanisms, HMGB1 is expected to have complex functions depending on the different conditions. Treatment targeting HMGB1 in the clinical setting may be useful in conditions like ALI and ARDS where inflammation itself has an adverse effect, but it may not necessarily be effective in ischemia and infarction where it is difficult to determine whether inflammation is beneficial or not.

**Effectiveness of Inflammation-Targeted Therapy**

It has been reported that steroid administration to MI patients from the acute phase increases the incidence of cardiac rupture,57 and massive administration of non-steroidal anti-inflammatory drugs promotes infarct expansion in animal experiments.58,59 These findings suggest that inflammation during the acute phase of MI is essential for the healing process that follows, and complete suppression of inflammation after infarction may lead to an adverse outcome. However, in an experiment in which a large dose of dexamethasone was administered before ischemia in a mouse IR model, favorable results were reported: adhesion of neutrophils to the vascular endothelium was inhibited, endothelial nitric oxide synthase was activated, and the infarct was smaller.60 These results suggest that anti-inflammatory drugs can work either way, to injure or to protect the myocardium, depending on timing and duration of administration, and the presence or absence of reperfusion.

In 2 clinical studies, the HALT-MI study,61 in which an antibody that blocks the CD11/CD18 integrin receptor involved in the attachment and transmigration of neutrophils was administered after PCI in patients with acute MI and a randomized controlled trial62 in which pexelizumab, a monoclonal antibody inhibiting complement (C5), was administered, no significant outcome regarding infarct size or clinical outcome was observed. In clinical studies, the demographic characteristics of patients and timing of reperfusion therapy vary. Therefore, it may be difficult to obtain a significant additional benefit by treatment targeting inflammation. However, in a recent study in which anakinra, an IL-1 receptor inhibitor, was administered to treat STEMI, a decrease in CRP, as well as improvement of LV remodeling on echocardiography or cardiac magnetic resonance imaging, was observed, even in a pilot study.63 Further results of this study are highly anticipated.

**Summary**

Inflammation and the immune response develop as a biological defense mechanism against trauma and infection. An excessive inflammatory response may be harmful for the healing process and cause pathological remodeling in aseptic necrotic tissue associated with ischemia. Therefore, inflammatory biomarkers could be used to stratify patients’ risk after MI. On the one hand, excessive inflammation by inflammatory monocytes/macrophages promotes LV remodeling after MI, while on the other hand, inflammation triggered by HMGB1 is a prerequisite for the healing process after MI. Therefore, appropriate control of inflammation is important. DCs constitute an important mechanism that regulates inflammatory, as well as anti-inflammatory, monocyte/macrophage homeostasis, and this is expected to be a new therapeutic target.

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**References**


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