Monocytosis and Adverse Left Ventricular Remodeling After Reperfused Myocardial Infarction*

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Over the last decade there has been growing interest in “bedside” protein and cellular markers of inflammation and adverse outcome after acute myocardial infarction (AMI) (1–16). In this issue of the Journal, Maekawa et al. (17) address the prognostic significance of peripheral monocytosis found at two to three days after reperfused AMI as a cellular marker for clinical outcome and its possible role in left ventricular (LV) remodeling.

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POSTINFARCT REMODELING AND ITS LIMITATION

It is recognized that LV remodeling after AMI is a major mechanism for cardiovascular death and disability (18,19). Ventricular remodeling and infarct healing are dynamic, time-dependent processes that progress in parallel (19). Healing after AMI involves inflammatory cell infiltrations followed by fibroblast proliferation, collagen deposition and remodeling in the infarct zone (19–22). Structural LV remodeling after AMI involves early regional infarct expansion (stretching, thinning and bulging) and progressive global LV dilation (18,19). Because structural LV remodeling spans phases of infarction and healing (19,22), therapy aimed at limiting structural LV remodeling can also be expected to influence healing (19). One algorithm, “salvage ischemic myocardium → preserve structure and shape → improve systolic squeeze → improve outcome and survival,” postulated more than a decade ago by several researchers (18,19,23,24), triggered several key trials (25–28) and studies (29) that established proof of the concept with antiremodeling therapy. There is general consensus that AMI is associated with an overexpression of the renin-angiotensin-aldosterone system that promotes structural LV remodeling, with angiotensin II (AngII) as the primary mediator (30), and inhibition of AngII formation with angiotensin-converting enzyme (ACE) inhibitors after AMI has proven to be very effective overall as antiremodeling therapy (25,27–29,31). Coronary reperfusion has also proven to be very effective overall in limiting structural LV remodeling (32–34) and accelerating healing (32) after AMI.

However, postinfarct remodeling is a complex process, and therapy targeted at one mechanism might produce previously unsuspected effects, some of which might be potentially deleterious (19). Thus, early use of some anti-inflammatory agents (35,36) were found to promote LV remodeling. Experimentally, ACE inhibitors were shown to inhibit infarct collagen deposition (37,38), which could potentially act as a “double-edged sword” and promote infarct remodeling, especially in the setting of large transmural infarction. Also experimentally, reperfusion results in reperfusion injury (39,40), damage to the supporting extra-cellular matrix (41) and necrosis (42). Ischemia-reperfusion has been shown to trigger the release of oxygen free radicals, cytokines and other mediators of inflammation (11). The latter activate neutrophils and endothelium, leading to recruitment of neutrophils to the endothelial surface, cell-to-cell interactions, adherence of neutrophils to endothelium, transendothelial migration and interaction with myocytes, causing injury. Several pharmacologic approaches directed against neutrophil after reperfused AMI, some of which implicated CD18, ICAM-1 and NFκ-B expression, have been tested and shown to limit infarct size (11). However, late reperfusion has several potential benefits (34,40). Whether the combination of late reperfusion and ACE inhibition might result in “double jeopardy” with respect to structural LV remodeling, especially in the setting of large transmural infarctions, has not been determined. Clearly, current pharmacotherapy after AMI is not ideal (19,43) because a significant number of post-MI patients develop progressive LV enlargement and heart failure, and many require heart transplantation and ventricular assist devices. Clinical markers (1,6–17) that can predict which patients are prone to develop adverse LV structural remodeling therefore would be very useful in prevention.

Role of inflammation in postinfarct remodeling. The similar association of inflammatory infiltrates in AMI (20) and unstable coronary plaques (14) has suggested that inflammation contributes to the pathogenesis of these syndromes. Clinical studies have demonstrated the presence of activated circulating neutrophils, lymphocytes and monocytes, increased levels of proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-alpha (TNF-α) and acute-phase reactants such as C-reactive protein (CRP) (14). Several studies have documented leukocytosis after AMI (6,11–15). In the Worcester Heart Attack Study (6) an elevated white blood cell (WBC) count correlated with in-hospital mortality and recurrent infarction. In the Studies Of Left Ventricular Dysfunction (SOLVD) study (12) a retrospective analysis revealed that the baseline WBC count was an independent predictor of mortality in patients with LV dysfunction. The WBC count after AMI was proposed for risk stratification of patients (15). An elevated neutrophil count was reported to correlate with pump failure after AMI (13). The procoagulant activity of peripheral monocytes and polymorphonuclear...
neutrophils after AMI was suggested to exacerbate the disease process (10).

The cellular response after AMI and reperfusion has been reviewed (2–6,11). Following AMI, neutrophils appear very early after reperfusion (11). Monocytes then migrate along the endothelial wall, interact with adhesion molecules and move into the infarct zone where they transform into macrophages, which become activated (17). Macrophages and monocytes outnumber neutrophils by two to three days (8,19). The macrophages and monocytes secrete factor-increasing monocytopoiesis, IL-6, macrophage colony stimulating factor (M-CSF) and monocyte chemoattractant protein-1 (MCP-1) (2,4). These monocyte-related cytokines lead to peripheral monocyteosis and monocyte infiltration of the infarct zone, suggesting that acute monocyte recruitment may be involved in infarct healing. Macrophages also secrete cytokines that stimulate fibroblast proliferation and collagen deposition, which are important during infarct healing. The monocyte-related cytokines (such as IL-1, IL-6 and TNF-α) stimulate liver cells to produce CRP. A correlation between IL-6 and serum CRP has been demonstrated in patients with AMI (3). Meisel et al. (8) found a correlation between peripheral monocyteosis and peak creatine kinase (CK) as an index of infarct size. In a study of patients with a first Q-wave AMI, Anzai et al. (7) found an association between CRP and infarct expansion, subacute cardiac rupture, LV aneurysm and adverse long-term outcome. In that study, both CRP and CK were higher in patients with pump failure, and reperfusion was defined as Thrombolysis In Myocardial Infarction (TIMI) flow grade 2 or more in the infarct-related vessel.

Monocytosis as a marker of adverse postinfarct remodeling. Maekawa et al. (17) studied a population consisting of 149 consecutive patients with a first Q-wave AMI who underwent primary percutaneous transluminal coronary angioplasty (PTCA) and received other therapies, including ACE inhibitors and beta-adrenergic blockers. Successful reperfusion was defined as restoration of TIMI flow grade 3 in the infarct-related artery without residual stenosis. The research team found that the peak monocyte count correlated positively with LV end-diastolic volume and negatively with ejection fraction on the predischarge left ventriculograms. Multivariate analysis revealed that a count ≥900/mm³ was an independent determinant of pump failure, LV aneurysm and cardiac events. The latter events included readmission for heart failure, recurrent infarction, cardiac deaths and sudden deaths. A positive correlation existed between the peak monocyte count and peak CK (r² = 0.076). On multiple logistic regression analysis, the peak monocyte count was an independent predictor of pump failure, whereas peak WBC count ≥12,000/mm³ and CK >3,000 IU/l were not. The investigators concluded that peripheral monocytosis is associated with LV dysfunction and LV aneurysm, suggesting a possible role in the development of LV remodeling.

This report by Maekawa et al. (17) also underscores the relevance of peripheral monocytosis in patients undergoing late reperfusion after AMI. The results support the idea that monocytosis might be linked to larger infarcts, bigger hearts and more LV dysfunction after reperfused AMI. The hypothesis that monocytosis might be involved in adverse LV remodeling and the suggestion that the magnitude of peripheral monocytosis might be a marker of adverse outcome and adverse LV remodeling after reperfused AMI are both clearly important. The investigators have been cautious in their conclusion as they have not established cause and effect. Furthermore, there are other major limitations in the study, such as the lack of a control group, the lack of data on the monocytes in the myocardium, and the small sample size. The investigators also had to exclude six of the original patients who died before the “peak monocyte count” could be measured. They also did not measure monocyte-related cytokines such as IL-6, MCSF-1 and MCP-1. Therefore, the researchers recognize that the data should be considered preliminary at this point and will require validation in further detailed studies and large clinical trials.

It is rather surprising in the study (17) that there was no correlation between monocytosis and the number of coronary artery vessels involved, frequency of stent implantation, and the use of ACE inhibitors or beta-blockers. The latter paradox, that neither ACE inhibition nor beta-blockade influenced the marker, may have been related to the timing of the measurements that were being correlated. For instance, both these drugs have long-term effects, but the evaluation of monocytosis was limited to the acute phase. Monocyte count was only measured at 2 ± 1 days. It is important to note that the patients were admitted 5 ± 5 h after the onset of AMI so that the reperfusion procedure was carried out late (within 6 ± 6 h of onset). The majority of patients (93%) were followed for more than 12 months (mean 33 ± 21 months), and the monocyte counts following admission were higher for patients who were readmitted with heart failure. If the monocyte count is a marker of bad LV remodeling, one would expect that the count during follow-up would detect the effect of therapies that are known to limit LV remodeling. In other words, the cellular marker should be able to differentiate between patients receiving and not receiving ACE inhibition if we accept the extensive evidence that the latter limits bad LV remodeling. However, the effect of ACE inhibition and beta blockade on the myocyte count was not evaluated.

It is important to note that in this study (17) late reperfusion with flow restoration to the TIMI-3 flow grade was still associated with fairly large (CK >3,000 IU/l in 56% of patients with pump failure and 35% with LV aneurysm) and transmural (in 100% of patients) AMI and significant adverse LV remodeling. This leads one to speculate that there was no significant salvage of an epicardial rim that might have offered some buttressing and structural support against infarct bulging (24,34,44). The strong correlation between monocytosis and adverse LV structural remodeling and outcome in this study suggests that inter-
ventions targeted against monocytes might be effective in prevention.

Also in this study (17), it is surprising that the correlation with peak CRP was so weak ($r^2 = 0.28$). However, data on another protein marker, the brain natriuretic peptide (BNP), albeit in a subgroup of 20 patients at seven days after anterior AMI, did show a good association. The plasma BNP was higher in those patients with peak monocyte count $\geq$900/mm$^3$, whereas peak CK was not different in patients with counts $>$ or $<$900/mm$^3$. Other investigators have described a good correlation between BNP levels and the LV end-diastolic volume (9).

Conclusions. The study by Maekawa et al. (17) addresses the utility of another marker of outcome after AMI. Although there are several limitations, this study focused on patients with late reperfused AMI, and all had successful PTCA with TIMI-3 flow grade. Importantly, this is the first study suggesting the potential role of monocytes in LV remodeling after reperfused AMI. Further studies are needed to establish whether peripheral myocytosis after reperfused AMI can predict patients prone to develop adverse LV remodeling.

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