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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# Inflammation as a Driver of Adverse Left Ventricular Remodeling After Acute Myocardial Infarction

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## ABSTRACT

Treatment of acute myocardial infarction (AMI) has improved significantly in recent years, but many patients have adverse left ventricular (LV) remodeling, a maladaptive change associated with progressive heart failure. Although this change is usually associated with large infarcts, some patients with relatively small infarcts have adverse remodeling, whereas other patients with larger infarcts (who survive the first several days after AMI) do not. This paper reviews the relevant data supporting the hypothesis that individual differences in the intensity of the post-AMI inflammatory response, involving 1 or more inflammatory-modulating pathways, may contribute to adverse LV remodeling. It concludes by outlining how individual variations in the inflammatory response could provide important novel therapeutic targets and strategies. (J Am Coll Cardiol 2016;67:2050–60) © 2016 by the American College of Cardiology Foundation.

Treatment of patients presenting with an acute myocardial infarction (AMI) has evolved enormously over the past several years. Percutaneous coronary intervention (PCI), when performed in the first hours after symptom onset, decreases acute mortality rates and reduces the incidence of compromised left ventricular (LV) function when measured within the first week after AMI (1). Although most patients treated by PCI within the recommended time frame also do well over the long term, in a subgroup of patients, progressive adverse LV remodeling and, ultimately, heart failure develop, despite implementation of secondary prevention measures, including beta-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, and aspirin. The traditional explanation for this phenomenon attributes it to high LV wall stress developing after a large AMI. Thus, the left ventricle dilates as a compensatory mechanism to improve LV pump function (through the Frank-Starling mechanism). LV dilation, by the Laplace relationship, increases wall stress, thus begetting further LV dilation. These changes, through a positive feedback loop, can lead to progressive adverse LV remodeling and to heart failure.

The purpose of this hypothesis-generating paper is 2-fold. The first is to review the relevant data indicating that the cause of adverse remodeling cannot be entirely ascribed to this traditional mechanistic view. This perspective is reinforced by newly analyzed (but previously published) data indicating that, in patients who survive the first several days of an AMI, a large infarct is *neither necessary nor sufficient* for progressive adverse LV remodeling to occur. This finding has important implications for the second purpose of this paper, which is to explore the hypothesis that

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persistently increased activation of inflammatory pathways importantly contributes to progressive adverse LV remodeling.

## IMPERFECT LINK BETWEEN INFARCT SIZE AND ADVERSE LV REMODELING

That infarct size is an important determinant of adverse remodeling has been demonstrated by several studies in which larger infarct size correlated with greater adverse LV remodeling. Thus, using LV ejection fraction (LVEF) determined by left ventriculography as an index of infarct severity, Schächinger et al. (2) demonstrated an inverse relationship between baseline LVEF (obtained 4 days post-AMI) and the increase in LV end-systolic volume (LVESV) and LV end-diastolic (LVEDV) volume measured 4 months later (**Figure 1**). Other investigators reported similar findings (3–5).

In addition to demonstrating that patients with reduced LVEF have a greater likelihood of developing progressive enlargement in LVESV and LVEDV over time, **Figure 1** also shows that a group of patients with normal or nearly normal LVEF several days after AMI can have progressively increased LVESV and LVEDV. Although the percentage of such patients with progressive dilation is considerably lower than that of the patients who start out with an abnormal LVEF, the number is notable. This finding suggests that mechanisms leading to adverse LV remodeling other than initial infarct size are in play.

LVEF, however, is not a precise measure of infarct size. In the context of decreased myocardial function, compensatory mechanisms attempt to maintain cardiac output. Impaired pump function leads, through the Frank-Starling mechanism, to increased LVEDV and thereby to increased myocardial fiber stretch. The increased stretch augments the force of contraction so that LVEF and cardiac output are maintained, despite the decreased LV pump function caused by a large infarct. Thus, LVEF may be maintained at nearly normal levels, despite a large infarct, consequent to the compensatory increase in LVEDV.

The relationship, or lack thereof, between infarct size and adverse LV remodeling can be approached more directly by data derived from cardiac magnetic resonance (CMR) imaging, which permits an estimate of infarct size through measurement of late gadolinium enhancement. **Figure 2** shows a new presentation of data from a study performed by 2 of the present authors (E.W. and R.B.) in which the relationship between baseline infarct size and subsequent adverse LV remodeling was compared (5). The data displayed in **Figure 2** were entered into spreadsheets and were extracted and reanalyzed so that the relationship between initial infarct size and absolute change in LVEDV could be specifically analyzed. CMR was performed within a week after ST-segment elevation myocardial infarction, with follow-up CMR 4 months later. Acute infarct size was a significant predictor of adverse cardiac remodeling: the greater the infarct size, the greater the subsequent increase in both LVEDV ($p < 0.001$) (**Figure 2**) and LVESV ($p = 0.001$). Moreover, in a multivariate analysis, infarct size more strongly predicted remodeling than did initial LVEF or LVESV.

This finding makes pathophysiological sense in terms of the Frank-Starling compensatory mechanism. In other words, the infarct-related decreased LV pump function puts into motion the conditions for progressive adverse LV remodeling. It follows that PCI, by rapidly restoring flow in the infarct-related artery, limits infarct size and thereby minimizes the risk of progressive LV remodeling and heart failure.

Careful examination of the data shown in **Figure 2**, which displays the relationship between adverse remodeling and actual infarct size, reveals that of the group of patients with 1) smaller infarct sizes (<18.5% of LV mass), in a subgroup of ~15%, progressive adverse LV remodeling (defined as an increase in LVEDV index of >10 ml/m$^2$) nonetheless developed; and 2) larger infarct sizes (≥18.5% of LV mass), approximately 40% had progressive adverse LV remodeling ($p = 0.008$), but therefore approximately 60% did not. Baseline differences (e.g., the presence of hypertension or hypercholesterolemia, tobacco smoking, diabetes, family history of coronary artery disease, among others) did not explain the differences in the amount of adverse remodeling between the patients with small infarcts and those with large infarcts.

This analysis raises the following questions: 1) if a large infarct is not a *necessary* cause of adverse remodeling, what then is the cause of the adverse remodeling in such patients? and 2) if a large infarct is not a *sufficient* cause of adverse remodeling, what accounts for the different propensity for adverse LV remodeling to develop in such patients?

The answers to these questions are undoubtedly complex and most likely involve multiple mechanisms. In this paper, we chose to focus on the experimental and clinical data suggesting that an excessive inflammatory response is, in addition to infarct size, a possible major contributor to the

### ABBREVIATIONS AND ACRONYMS

**AMI** = acute myocardial infarction

**CMR** = cardiac magnetic resonance

**CRP** = C-reactive protein

**IFN** = interferon

**IL** = interleukin

**LV** = left ventricular

**LVEDV** = left ventricular end-diastolic volume

**LVEF** = left ventricular ejection fraction

**LVESV** = left ventricular end-systolic volume

**MMP** = matrix metalloproteinase

**MSC** = mesenchymal stem cell

**PCI** = percutaneous coronary intervention

**ROS** = reactive oxygen species

**TGF** = transforming growth factor

**TIMP** = tissue inhibitor of metalloproteinases

**TNF** = tumor necrosis factor