Oxidative Stress and Cardiac Repair/Remodeling Following Infarction

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ABSTRACT: Extensive cardiac remodeling after myocardial infarction (MI) contributes significantly to ventricular dysfunction. Factors regulating left ventricular remodeling at different stages after MI are under investigation. There is growing recognition and experimental evidence that oxidative stress mediated by reactive oxygen species plays a role in the pathogeneses of myocardial repair/remodeling in various cardiac diseases. After acute MI, oxidative stress is developed in both infarcted and noninfarcted myocardium. Accumulating evidence has demonstrated that oxidative stress participates in several aspects of cardiac repair/remodeling after infarction that include cardiomyocyte apoptosis, inflammatory/fibrogenic responses, and hypertrophy. The exact pathways on reactive oxygen species–mediated myocardial remodeling are under investigation. The therapeutic potential of oxidative stress-directed drugs in myocardial remodeling after infarction has not been fully realized. **KEY INDEXING TERMS:** Oxidative stress; Myocardial infarction; Myocardial repair; Myocardial remodeling. **[Am J Med Sci 2007;334(3):197–205.]**

Heart failure has emerged as a major health problem during the past 2 decades. It appears most commonly in patients with previous myocardial infarction (MI). Myocardial remodeling, which occurs in both infarcted and noninfarcted myocardium, contributes significantly to the development of heart failure.[1–3] After MI, cardiac structural remodeling is associated with an inflammatory reaction, which is followed by scar formation at the site of infarction and hypertrophy with interstitial fibrosis and vascular remodeling in noninfarcted myocardium. This leads to ventricular remodeling characterized by alterations in left ventricular size, shape, and wall thickness.[4–6] Fibrous tissue that forms at the site of cardiomyocyte loss preserves the structural integrity and is integral to the heart's recovery, whereas the structural remodeling of viable myocardium impairs tissue behavior. Multiple factors may, in fact, contribute to left ventricular remodeling at different stages after MI. There is experimental evidence to suggest that oxidative stress mediated by reactive oxygen species (ROS) plays a role in the pathogeneses of myocardial repair/remodeling after MI, a hypothesis that has been earning growing recognition.[7–11] Oxidative stress results from an oxidant/antioxidant imbalance: an excess of oxidants relative to the antioxidant capacity. The heart with acute MI undergoes an increased ROS production as well as antioxidant deficit, first in the infarcted myocardium, followed by the noninfarcted myocardium. Chronic antioxidant treatment suppresses cardiac oxidative stress, attenuates ventricular remodeling, partially preserving left ventricular function and improved survival in rats or mice with experimental MI.[12–14] Experimental studies have also demonstrated that oxidative stress can induce most, if not all, of the changes that are thought to contribute to myocardial remodeling including proinflammatory cytokine release, cardiomyocyte apoptosis,[15] fibrogenesis,[16] cell proliferation,[17,18] and hypertrophy.[19] In this brief review, the potential relevance of oxidative stress on apoptosis, inflammatory/fibrogenic responses, hypertrophy, and cardiac dysfunction in the infarcted heart will be discussed. The role of antioxidants in cardiac remodeling and dysfunction will be also discussed.

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Oxidative Stress in the Infarcted Heart

Superoxide (O_2^-), hydroxyl (OH^-), and peroxynitrite ($ONOO^-$) are simple molecules characterized by the presence of unpaired electrons. ROS can be produced intracellularly through electron leakage from mitochondria during oxidative phosphorylation and through the activation of several cellular enzymes, including NADPH oxidase, xanthine oxidase, and nitric oxide synthase.[20–22] O_2^- can rapidly react with nitric oxide (NO) to form $ONOO^-$ or convert to H_2O_2 to form OH^-.[20] ROS in low concentrations serve as signaling molecules.[23] However,

these agents elicit harmful effects when produced in excess.[20] The toxicity associated with the excessive production of these compounds is prevented by antioxidant defense systems that maintain a healthy cellular environment. Living cells have both enzymatic and nonenzymatic defense mechanisms to balance the multitude of oxidative challenges presented to them. The enzymatic subgroup includes superoxide dismutase (SOD), catalase and glutathione peroxidase (GSHPx).[24–26] The dismutation of O_2^- by SOD results in the generation of H_2O_2, which catalase further metabolizes into water and oxygen. The nonenzymatic group includes a variety of biologic molecules, such as vitamins E and C.[27] Oxidative stress occurs when ROS production is enhanced and/or antioxidant reserve is suppressed.

In the myocardium, as in other tissues, antioxidant enzymes protect cells by maintaining O_2^- and H_2O_2 at low levels. After MI, oxidative stress is developed in both infarcted and noninfarcted myocardium. Singal and colleagues[7,28] have shown the evidence of progressive decrease in SOD, catalase and GSHPx activity as well as vitamin E levels in the rat infarcted heart, first in the infarcted myocardium, followed by noninfarcted myocardium. Our study has shown reduced SOD gene and protein expression in the infarcted myocardium[29] (see Figure 1). Cardiac glutathione levels are also decreased in patients with acute MI.[30] These observations raise the possibility that impaired antioxidant capacity contribute to oxidative stress in the infarcted heart. NADPH oxidase is a major source of O_2^- in the heart.[31] In the infarcted heart, NADPH oxidase expression ($gp22^{phox}$ and $gp91^{phox}$ subunits) is significantly increased in the infarcted myocardium,[29,32] with neutrophils and macrophages as the primary cells expressing the enzyme (see Figure 1). These findings suggest that ROS production is also enhanced in the infarcted myocardium. Malondialdehyde (MDA) is an end product in the lipid peroxidation chain reaction and is frequently used as a marker for ROS production. Our study has shown that MDA level is significantly increased in the infarcted myocardium (see Figure 1). This observation further confirmed enhanced cardiac ROS production after infarction. Moreover, 3-nitrotyrosine, a marker of oxidative stress, is highly expressed in the inflammatory cells of the infarcted myocardium, supporting the occurrence of cardiac oxidative stress after MI[29] (see Figure 1). Oxidative stress in noninfarcted myocardium is contributed by multiple sources. Increased mitochondrial production of ROS has been suggested in noninfarcted myocardium of mice as one of them.[33] Increased ROS levels in noninfarcted myocardium also reflect increased activity of intracellular oxidase complexes, such as NADPH oxidase, xanthine oxidase, and nitric oxide synthase.[34] In addition, reduced SOD levels were observed in the failing heart with infarction.[35] These observations indicate that the imbalance between ROS production and antioxidant defense capacity contribute to oxidative stress in noninfarcted myocardium.

Oxidative Stress and Cardiomyocyte Apoptosis in the Infarcted Heart

Loss of cardiomyocytes is an important mechanism in the development of myocardial remodeling and cardiac failure.[36] After MI, apoptotic cardiomyocyte death occurs in the infarcted myocardium as well as the surviving portions of the wall adjacent to and remote from the infarcted myocardium.[37,38] However, the number of apoptotic cardiomyocytes is greater in the infarcted region than in the region away from infarction. The regulation of cardiomyocyte apoptosis involves multiple mechanisms. ROS have been proven to be one of the stimulators of cardiomyocyte apoptosis.[39–43] High levels of oxidative stress have been demonstrated to cause cell necrosis, whereas lower levels of oxidative stress can cause cell apoptosis. *In vitro* studies have shown that treatment with O_2^- or H_2O_2 in cardiomyocytes induces apoptosis.[44] *In vivo* studies have further demonstrated that oxidative stress triggers cardiomyocyte apoptosis in several cardiovascular diseases, including MI, ischemia/reperfusion injury, cardiomyopathy, atherosclerosis and heart failure.[45–51] Long-term treatment with the antioxidants probucol or pyrrolidine dithiocarbamate attenuates oxidative stress and cardiomyocyte apoptosis within noninfarcted myocardium in rats.[13,40] Another antioxidant, carvedilol, is shown to attenuate apoptosis induced by ischemia-reperfusion in the rat heart.[52] Oxidant scavengers, such as SOD and vitamin E, have been demonstrated to reduce ROS and inhibit cardiomyocyte apoptosis.[53]

The mechanisms responsible for oxidative stress-mediated apoptosis in the infarcted heart are not fully understood. Multiple studies have shown that ROS can induce cardiomyocyte death by one or more mechanisms. Apoptosis is tightly controlled by a number of genes, including those primarily suppressing and those promoting apoptosis. Our previous studies identified markedly increased proapoptotic *Bax* expression in the infarcted heart, particularly at the site of infarction (see Figure 2). Enhanced Bax expression coexists with oxidative stress and apoptosis in the infarcted heart.[54] Overexpression of anti-apoptotic *Bcl-2* decreases cardiomyocyte apoptosis.[55] Cesselli et al[56] have shown that in dog dilated cardiomyopathy, oxidative stress-induced cardiac apoptosis is related to increased $p66^{she}$, cytochrome c release, and activation of caspase-9 and caspase-3. Taken together, these findings suggest that oxidative stress may trigger cardiomyocyte apoptosis via regulation of apoptotic genes.

Cytokines, such as tumor necrosis factor (TNF)-α and interleukin-6, are proven to stimulate cardiomy-