Cardioprotection of Insulin-Like Growth Factor-1 During Reperfusion Therapy
What Is the Underlying Mechanism or Mechanisms?

Wangde Dai, MD; Robert A. Kloner, MD, PhD

In the setting of acute myocardial infarction, reperfusion of ischemic myocardium carried out early after coronary occlusion can salvage reversibly injured, viable myocardium. Although still controversial, however, reperfusion itself may cause a population of reversibly injured cells to die, a phenomenon termed lethal reperfusion injury.1 A variety of pharmacological agents have been studied to limit ischemia/reperfusion injury as an adjunct to current reperfusion, and some beneficial effects have been demonstrated in experimental animal research, but their clinical applications have not been achieved.2–4

Among the various agents claimed to have cardioprotective effects is insulin-like growth factor-1 (IGF-1), which is a hormone produced primarily by the liver. Its molecular structure is similar to that of insulin. IGF-1 plays an important role in cellular survival and growth by binding to its specific receptor (IGF1R), which is present on many cell types, including cardiac cells. Activation of IGF1R, a receptor tyrosine kinase, has been demonstrated to attenuate both apoptotic and necrotic cell death induced by ischemia/reperfusion injury through stimulation of both intracellular phosphoinositide 3-kinase/protein kinase B signaling pathway and extracellular signal-regulated kinase 1/2 signaling cascades.5 Buerke et al6 administered IGF-I 1 hour before ischemia in a murine model of 20 minutes of myocardial ischemia followed by 24 hours of reperfusion. IGF-I preserved ischemic/reperfused myocardium through inhibition of polymorphonuclear leukocyte-induced cardiac necrosis and inhibition of reperfusion-induced apoptosis of cardiac myocytes. Davani et al7 subjected isolated murine hearts to 20 minutes of global ischemia followed by 2 hours of reperfusion with either modified Kreb’s solution alone or Kreb’s solution plus IGF-1. IGF-1, which was administrated immediately after reperfusion, protected ischemic myocardium from further reperfusion injury through mitochondria-dependent mechanisms characterized by maintenance of the ratio of mitochondria to nDNA within heart tissue.

As reported in this issue of Circulation: Cardiovascular Interventions, O’Sullivan et al8 induced ischemia/reperfusion in pigs by balloon occlusion of the mid-left anterior descending coronary artery for 90 minutes followed by 2 hours of reperfusion. At the end of the 2 hours of reperfusion, IGF-1 or saline only was delivered to the ischemic area through an intracoronary route. At 30 minutes after treatment, IGF-1 increased the activation of IGF-1 receptor as well as the activation of protein kinase B, extracellular signal-regulated kinase, and glycogen synthase kinase-3β, which are the signaling pathways downstream of IGF1R activation. At 24 hours after treatment, IGF-1 significantly reduced apoptosis of cardiomyocytes within the infarct zone as assessed by TUNEL staining and caspase-9 activity within the ischemic border zone. At 2 months after treatment, IGF-1 reduced infarct size, infarct collagen content, and fibrotic markers; increased cardiomyocyte number within the infarct zone; improved regional wall motion; thickened the infarct wall; and improved global left ventricular remodeling and function. The authors suggested that the mechanism of the cardioprotective effects of IGF-1 was through the activation of signaling, downstream of IGF1R, affecting both membrane pore transition and caspase pathways. A rather remarkable feature of this study was that the authors observed a protective effect of IGF-1 even when it was administered relatively late after the onset of reperfusion. Previously, studies on ischemic postconditioning9 suggested that if reperfusion injury exists, it occurs within the first few minutes of reperfusion (in that reocclusion as part of a postocclusion protocol must occur within seconds or minutes to have a protective effect). The finding that an agent can be given as late as 2 hours after reperfusion and still reduce infarct size is rather surprising. This finding should be verified by other groups, and if true, it has important implications and suggests that the window for salvaging ischemic/reperfused myocardium may be much wider than previously believed. The finding that low-dose IGF-1 reduced this necrosis at least in part by reducing apoptosis suggests that apoptosis on reperfusion, a phenomenon known for some time,10 may account for considerably more cardiac cell death than appreciated in the past. The finding also raises the issue of whether even earlier administration of IGF (at or within minutes of reperfusion) would have resulted in an even greater degree of salvage of ischemic/reperfused myocardium.

Another important finding by O’Sullivan et al8 was that IGF reduced long-term left ventricular remodeling and im-

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From The Heart Institute of Good Samaritan Hospital and Division of Cardiovascular Medicine of the Keck School of Medicine, University of Southern California, Los Angeles, CA.

Correspondence to Wangde Dai, MD, The Heart Institute of Good Samaritan Hospital, 1225 Wilshire Blvd, Los Angeles, CA 90017. E-mail Wangdedai@yahoo.com

(Circ Cardiovasc Inter. 2011;4:311-313.)

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Circ Cardiovasc Inter is available at http://circinterventions.ahajournals.org
DOI: 10.1161/CIRCINTERVENTIONS.111.964049
IGF-1 was suggested to exert favorable effects on angiogenesis after myocardial infarction. Therefore, in the study by O’Sullivan et al., it is possible that IGF-1 contributed to the viability and growth of these endogenous cardiac stem cells and cardiomyogenesis as well as angiogenesis within the damaged area. This regenerative capability of IGF-1 may have helped to explain the reduced infarct scar, reduced left ventricular remodeling, and improved cardiac function independent of any acute reduction in infarct size.

However, not all studies that have injected such growth hormones have been positive. Recently, Hwang and Kloner ligated the left coronary artery and injected fibroblast growth factor-2, IGF-1, hepatocyte growth factor, and stromal cell-derived factor-1α directly into the ischemic myocardium at the onset of coronary occlusion in rats. Subsequently, the 4 factors were administrated intraperitoneally at 3, 7, 14, and 21 days after surgery. At 4 weeks after myocardial infarction, treatment with growth factors did not enhance cardiac function, reduce infarct size, and improve remodeling, or increase vasculature density compared with controls treated with saline. Scheinowitz et al. also reported that continuous infusion (for 1 week after acute myocardial infarction) of IGF-1, basic fibroblast growth factor, or IGF-1 plus basic fibroblast growth factor did not affect left ventricular geometry after myocardial infarction. The Table summarizes various published
studies that have examined the effects of IGF-1 on experimental myocardial infarction.

In summary, the study by O’Sullivan et al demonstrates that IGF-1 is a promising agent to prevent ischemia/reperfusion injury as an adjunct to reperfusion of ischemic myocardium. Future investigations are necessary to identify the precise underlying mechanism or mechanisms of this observed potent cardioprotective strategy whether through influencing the apoptotic signaling pathway of adult cardiac cells, by inducing cardiomyogenesis from endogenous cardiac stem cells and angiogenesis, or through both. To maximize the therapeutic effects, the dosing and timing of administration should be investigated further.

Disclosures
None.

References

Key Words: Editorials | myocardial infarction | apoptosis | IGF-1
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*Circ Cardiovasc Interv.* 2011;4:311-313
doi: 10.1161/CIRCINTERVENTIONS.111.964049
*Circulation: Cardiovascular Interventions* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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