

## Cardioprotection of Insulin-Like Growth Factor-1 During Reperfusion Therapy

### What Is the Underlying Mechanism or Mechanisms?

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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*.<sup>1</sup> 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.<sup>2-4</sup>

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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 stimulating both the intracellular phosphoinositide 3-kinase/protein kinase B signaling pathway and extracellular signal-regulated kinase 1/2 signaling cascades.<sup>5</sup> Buerke et al<sup>6</sup> administered IGF-1 1 hour before ischemia in a murine model of 20 minutes of myocardial ischemia followed by 24 hours of reperfusion. IGF-1 preserved ischemic/reperused myocardium through inhibition of polymorphonuclear leukocyte-induced cardiac necrosis and inhibition of reperfusion-induced apoptosis of cardiac myocytes. Davani et al<sup>7</sup> subjected isolated murine hearts to 20 minutes of global ischemia followed by 2 hours of reperfusion with either modified Krebs's solution alone or Krebs's solution plus IGF-1. IGF-1, which was administered 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 al<sup>8</sup> 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-3 $\beta$ , 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 postconditioning<sup>9</sup> 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 postreperfusion 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/reperused 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,<sup>10</sup> 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 a greater degree of salvage of ischemic/reperused myocardium.

Another important finding by O'Sullivan et al<sup>8</sup> was that IGF reduced long-term left ventricular remodeling and im-

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**Table. Summary of Therapeutic Effects of IGF-1 in Experimental Myocardial Infarction**

Studies	Animal Model	Duration of Follow-Up	Therapeutic Effects
Buerke et al <sup>6</sup>	20 min of coronary artery occlusion followed by 24 h reperfusion in mouse	24 h	IGF-1 preserved ischemic/reperfused myocardium through inhibition of polymorphonuclear leukocyte-induced cardiac necrosis and inhibition of reperfusion-induced apoptosis of cardiac myocytes.
Davani et al <sup>7</sup>	20 min of global ischemia followed by 2 h of reperfusion in isolated mouse hearts	2 h	IGF-1 protected ischemic myocardium from further reperfusion injury through mitochondria-dependent mechanisms.
O'Sullivan et al <sup>8</sup>	90 min of coronary artery occlusion followed by reperfusion in pigs	2 mo	IGF-1 significantly reduced apoptosis of cardiomyocytes within the infarct zone, 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.
Urbanek et al <sup>11</sup>	Ligation of the left coronary artery in mice	4 mo	IGF-1 improved the viability and growth of host cardiac stem cells within the damaged area.
Padin-Iruegas et al <sup>12</sup>	Ligation of the left coronary artery in rats	1 mo	IGF-1 enhanced cardiac repair after infarction through potentiating the activation and differentiation of delivered and resident cardiac progenitor cells.
Dobrucki et al <sup>13</sup>	Ligation of the left coronary artery in rats	16 wk	IGF-1 expression was associated with a remarkable increase in capillary density and improvement in cardiac function.
Hwang and Kloner <sup>14</sup>	Ligation of the left coronary artery in rats	4 wk	IGF-1 plus other factors did not enhance cardiac function, reduce infarct size, and improve remodeling.
Scheinowitz et al <sup>15</sup>	Ligation of the left coronary artery in rats	6 wk	IGF-1 plus basic fibroblast growth factor did not affect left ventricular geometry after myocardial infarction.

IGF-1 indicates insulin-like growth factor-1.

proved cardiac function. The early reduction in infarct size and reduction in apoptosis may be the mechanism. However, a second mechanism may have been involved that is independent of infarct size reduction. The heart has an endogenous reserve of cardiac stem cells that express IGF1R. In a mouse myocardial infarction model, Urbanek et al<sup>11</sup> injected IGF-1 and hepatocyte growth factor into the infarcted myocardium and observed that the volume of regenerated myocytes significantly increased at 4 months after treatment. Nearly 20% of regenerated myocytes reached the adult phenotype. The data suggested that hepatocyte growth factor favored the translocation of cardiac stem cells from the surrounding myocardium to the dead tissue, and IGF-1 improved the viability and growth of these cells within the damaged area. Padin-Iruegas et al<sup>12</sup> induced myocardial infarction in rats. The rats received local injection of cardiac progenitor cells or IGF-1 only or cardiac progenitor cells plus IGF-1. Newly formed cardiomyocytes were detected in all treated infarcts, although combination therapy resulted in a greater increase in myocardial regeneration. IGF-1 enhanced cardiac repair after infarction through potentiating the activation and differentiation of delivered and resident cardiac progenitor cells. Dobrucki et al<sup>13</sup> induced myocardial infarction in rats by ligation of the left coronary artery and injected human IGF-1 gene around the periinfarct area by adeno-associated virus. At 16 weeks after gene delivery, higher IGF-1 expression was associated with a remarkable increase in capillary density and improvement in cardiac function.

IGF-1 was suggested to exert favorable effects on angiogenesis after myocardial infarction. Therefore, in the study by O'Sullivan et al,<sup>8</sup> 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<sup>14</sup> ligated the left coronary artery and injected fibroblast growth factor-2, IGF-1, hepatocyte growth factor, and stromal cell-derived factor-1 $\alpha$  directly into the ischemic myocardium at the onset of coronary occlusion in rats. Subsequently, the 4 factors were administered 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, improve remodeling, or increase vasculature density compared with controls treated with saline. Scheinowitz et al<sup>15</sup> 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 at 6 weeks after myocardial infarction in rats. The results do not support the hypothesis that the combined use of multiple soluble growth factors benefits the hearts with myocardial infarct. 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<sup>8</sup> 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

- Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? *J Clin Invest.* 1985;76:1713–1719.
- Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. *Catheter Cardiovasc Interv.* 2008;72:950–957.
- Reffelmann T, Kloner RA. Phosphodiesterase 5 inhibitors: are they cardioprotective? *Cardiovasc Res.* 2009;83:204–212.
- Dai W, Kloner RA. Potential role of renin-angiotensin system blockade for preventing myocardial ischemia/reperfusion injury and remodeling after myocardial infarction. *Postgrad Med.* 2011;123:49–55.
- Hausenloy DJ, Yellon DM. New directions for protecting the heart against ischaemia-reperfusion injury: targeting the Reperfusion Injury Salvage Kinase (RISK)-pathway. *Cardiovasc Res.* 2004;61:448–460.
- Buerke M, Murohara T, Skurk C, Nuss C, Tomaselli K, Lefer AM. Cardioprotective effect of insulin-like growth factor I in myocardial ischemia followed by reperfusion. *Proc Natl Acad Sci U S A.* 1995;92:8031–8035.
- Davani EY, Brumme Z, Singhera GK, Côté HC, Harrigan PR, Dorscheid DR. Insulin-like growth factor-1 protects ischemic murine myocardium from ischemia/reperfusion associated injury. *Crit Care.* 2003;7:R176–R183.
- O'Sullivan JF, Leblond AL, Kelly G, Kumar AHS, Metharom P, Büneker CK, Alizadeh-Vikali N, Hristova I, Hynes BG, O'Connor R, Caplice NM. Potent long-term cardioprotective effects of single low-dose insulin-like growth factor-1 (LD-IGF-1) treatment postmyocardial infarction. *Circ Cardiovasc Interv.* 2011;4:327–335.
- Kin H, Zhao ZQ, Sun HY, Wang NP, Corvera JS, Halkos ME, Kerendi F, Guyton RA, Vinten-Johansen J. Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early minutes of reperfusion. *Cardiovasc Res.* 2004;62:74–85.
- Gottlieb RA, Burleson KO, Kloner RA, Babior BM, Engler RL. Reperfusion injury induces apoptosis in rabbit cardiomyocytes. *J Clin Invest.* 1994;94:1621–1628.
- Urbanek K, Rota M, Cascapera S, Bearzi C, Nascimbene A, De Angelis A, Hosoda T, Chimenti S, Baker M, Limana F, Nurzynska D, Torella D, Rotatori F, Rastaldo R, Musso E, Quaini F, Leri A, Kajstura J, Anversa P. Cardiac stem cells possess growth factor-receptor systems that after activation regenerate the infarcted myocardium, improving ventricular function and long-term survival. *Circ Res.* 2005;97:663–673.
- Padin-Iruegas ME, Misao Y, Davis ME, Segers VF, Esposito G, Tokunou T, Urbanek K, Hosoda T, Rota M, Anversa P, Leri A, Lee RT, Kajstura J. Cardiac progenitor cells and biotinylated insulin-like growth factor-1 nanofibers improve endogenous and exogenous myocardial regeneration after infarction. *Circulation.* 2009;120:876–887.
- Dobrucki LW, Tsutsumi Y, Kalinowski L, Dean J, Gavin M, Sen S, Mendizabal M, Sinusas AJ, Aikawa R. Analysis of angiogenesis induced by local IGF-1 expression after myocardial infarction using microSPECT-CT imaging. *J Mol Cell Cardiol.* 2010;48:1071–1079.
- Hwang H, Kloner RA. The combined administration of multiple soluble factors in the repair of chronically infarcted rat myocardium. *J Cardiovasc Pharmacol.* 2011;57:282–286.
- Scheinowitz M, Abramov D, Kotlyar A, Savion N, Eldar M. Continuous administration of insulin-like growth factor-I and basic fibroblast growth factor does not affect left ventricular geometry after acute myocardial infarction in rats. *Int J Cardiol.* 1998;63:217–221.

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