New therapies for reducing post-myocardial left ventricular remodeling

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Current therapies for myocardial infarction are geared to try to limit ischemic/reperfusion injury by early and complete reperfusion, including percutaneous coronary interventions, antiplatelet agents, and anticoagulants; and attempts to limit post infarction left ventricular remodeling by inhibitors of the renin-angiotensin-aldosterone pathway or administration of beta blockers. Despite wide use of these therapies, 30-day mortality still runs 7-8% and one year mortality runs around 23% (1). There clearly is an unmet need to further improve outcomes after myocardial infarction. One important target includes improving the healing phase of myocardial infarction. Following the development of myocardial necrosis due to ischemia/reperfusion, the friable area of necrosis stretches and thins as collagen struts that normally maintain the interstitial architecture, degenerate. Matrix metalloproteinases are enzymes that may contribute to this process. The thinning and stretching of the scar is termed infarct expansion and can be observed in experimental animal models within the first week of coronary occlusion (2). Infarct expansion has also been observed in clinical studies within the first week of infarction as assessed by noninvasive imaging such as echocardiography (3). As the infarct expands, the entire left ventricle dilates, increasing wall stress. Eccentric hypertrophy of the noninfarcted walls occurs, further altering left ventricular geometry. The entire process of infarct expansion, left ventricular dilatation and eccentric hypertrophy is termed post myocardial infarction left ventricular remodeling (4). Patients that exhibit this phenomenon are more likely to experience adverse cardiac events including death and heart failure. While angiotensin converting enzyme inhibitors, angiotensin receptor blockers and certain beta blockers help to reduce remodeling and improve clinical outcome, the overall reduction of events is modest and runs around 20-25% (5). So again, new therapies are needed to reduce remodeling post infarction.

What are some of the newer therapies that have shown benefit? One type of therapy that has shown promise is the injection of certain types of stem cells or immature cardiomyocytes within the first week of myocardial infarction. Previous work from our group showed that injection of neonatal or fetal cardiomyocytes into a one week old experimental myocardial infarct in a rat model reduced left ventricular remodeling many months after the acute coronary occlusion, including improving wall thickness of the scar, reducing infarct expansion, reducing left ventricular dilatation and improving long term ejection fraction (6,7). Similar improvements were observed when embryonic stem cell derived cardiomyocytes were injected at one week into a rat model of proximal left coronary artery occlusion (8). Several meta-analyses of stem cell therapy in humans have also suggested a reduction of left ventricular remodeling, including decreases in end-diastolic and end-systolic left ventricular volumes and modest improvements in left ventricular ejection fraction. There is ongoing discussion regarding whether these benefits are truly due to replacement of cardiac muscle with exogenous cells that have taken on a cardiac phenotype or are due to a paracrine mechanism, or perhaps both. In our early studies in which immature heart cells were injected, grafts with sarcomeres could be visualized, suggesting that at least in these studies the benefits were not solely due to a paracrine effect (6,7). However, when we used bone marrow derived mesenchymal stem cells, we did not see well delineated muscle grafts late after infarction, but we did observe an increase in angiogenesis and a transient improvement of

ejection fraction. In this case, a paracrine effect may have been very important (9,10). Although cell-based clinical trials to treat myocardial infarction using skeletal myoblasts, bone marrow derived stem cells and cardio-sphere derived stem cells have shown that delivery of cells into diseased hearts is feasible and safe (11,12), there are still many challenges and unanswered questions that remain to be resolved before the clinical application of cell therapy becomes routine clinical therapy. There is a need to find the best way to increase retention and long-term survival of engrafted cells within the host heart, and to determine how to induce the engrafted cells to truly differentiate into mature adult cardiac cells and integrate with host cardiac cells to simultaneously contract. In addition, there is a need to determine the optimal numbers and types of cells to inject as well as the optimal route and timing of delivery of these cells after myocardial infarction (13). Another limitation of cell therapy is that only a moderate increase in left ventricular ejection fraction of 3-6% over time compared with control patients was observed; the effects of cell therapy must be compared with established therapeutic strategies such as reperfusion therapy, pharmacological interventions or noncellular biomaterial implantation into the injured heart (14,15).

Another approach besides injecting cells into the scar is to thicken the scar and try to prevent infarct expansion using non cellular material. The idea here is that by increasing mass within the scar, even using inert substances, that wall stress will be reduced and infarct expansion diminished. Previously, Dai in our group showed that injecting collagen (similar to the kind that is used for cosmetic surgery of the skin) thickened the infarct scar and improved long term left ventricular ejection fraction. A second study using interstitial matrix material showed similar results (15). Hence injecting non cellular material resulted in some of the same benefits as injecting cells. One difference is that injecting cells usually resulted in increased vascularization to the wall of the heart, whereas injecting non cellular material did not have this benefit. There are clinical studies ongoing looking at the effect of injecting non cellular materials such as alginate into the coronary arteries of patients. The alginate is injected as a liquid and then hardens at the tissue level where it may prevent infarct expansion and adverse remodeling (16).

There have also been advances in the pharmacologic therapy of adverse post infarction left ventricular remodeling. One novel approach has been to target the mitochondria with an experimental agent called Bendavia. Bendavia is a small peptide that localizes to the inner mitochondrial membrane where it is thought to stabilize cardiolipin, improve electron transport and reduce the production of toxic reactive oxygen species. In an experimental model in which Bendavia was administered starting 2 hours after proximal left coronary artery occlusion in the rat, and continued for 6 weeks of therapy via an osmotic pump delivery system, the drug reduced left ventricular volume, scar circumference and improved left ventricular ejection fraction compared to controls (17). In addition, Bendavia improved the function of the electron transport chain, reduced apoptosis, and reduced hypertrophy in the non-infarcted border zone. Importantly, Bendavia has no effect on heart rate or blood pressure, unlike angiotensin converting inhibitors, angiotensin receptor blockers or beta blockers, currently being used to improve post infarction outcomes. This is important as many patients who are on the standard drugs used post infarction or for heart failure develop hypotension and bradycardia, and cannot tolerate these agents in high doses. While existing agents primarily work to reduce myocardial workload, Bendavia works to protect the energy producing mechanism of the cell.

In general, agents that reduce myocardial infarct size during that acute phase of infarction will reduce later left ventricular remodeling. For example, in experimental models of acute myocardial infarction in the rat, we observed that hypothermia started during the ischemic period markedly reduced the size of the heart attack when measured a few hours after reperfusion. When hearts were assessed 6 weeks later, hypothermia had markedly reduced scar circumference and left ventricular volumes and was associated with a much improved ejection fraction (18). However in the examples given above (immature heart cells, stem cells, Bendavia) the therapies were given too late to have a direct effect on infarct size, and any benefit was derived from later effects on preventing infarct expansion and remodeling (18).

A very intriguing method for reducing left ventricular remodeling was recently published in an article by Eckhouse *et al*. in *Science Translational Medicine*, Feb 12, 2014 entitled "Local hydrogel release of recombinant TIMP-3 attenuates adverse left ventricular remodeling after experimental myocardial infarction" from the well-known laboratories of Dr. Spinale, Gorman and others (19). The investigators delivered regional tissue inhibitor of matrix metalloproteinases (MMP) using hydrogel as a delivery system. They injected degradable hydrogel directly into pig hearts after subjecting the hearts to occlusions of the

obtuse marginal branches of the circumflex coronary artery. They measured a host of parameters over the course of 14 days in sham pigs (no infarction), pigs infarcted but treated with saline, pigs treated with injection of hydrogel, and pigs injected with hydrogel delivering rTIMP-3 (Tissue inhibitor of metalloproteinase 3). They used sophisticated measures of tracking cardiac function including echocardiography, fluoroscopy and cardiac magnetic resonance imaging. Pigs that received the combination of hydrogel plus rTIMP-3 had improved left ventricular ejection fraction, reduced ventricular dilatation, and reduced infarct expansion. Of note, hydrogel alone had some beneficial effects on certain parameters such as wall stress and myocardial infarct area but hydrogel plus rTIMP-3 appeared to be better. Interstitial MMP activity was increased in the saline and hydrogel control groups compared to sham (no infarct) pigs. However, in the hydrogel-rTIMP3 group MMP levels were reduced to levels similar to sham pigs and TIMP-3 tissue levels were increased. C-reactive protein levels were reduced in both the hydrogel and the hydrogel-rTIMP3 groups compared to infarcted pigs treated with saline. Interlukin-8 and the macrophage marker CD44 antigen-like were reduced in the hydrogel plus rTIMP-3 group as were other markers of inflammation. In addition, hydrogel-rTIMP-3 increased indices of myofibroblast density. The authors are to be congratulated on a fine and detailed study clearly showing that local injection of hydrogel containing rTIMP-3 had beneficial effects on the healing phase of myocardial infarction, preventing infarct expansion, reducing left ventricular dilatation and improving left ventricular ejection fraction. They used a large animal model and this therapy should be adaptable to the clinical setting. In humans it is not likely that direct injections into the heart will be done in this fashion (unless the patient is undergoing surgical revascularization for myocardial infarction) but certainly there are percutaneous techniques that have been used to allow intramyocardial injections via a catheter in the left ventricular cavity. Injections of stem cells by such a technique are well known. Since the mechanism of action is unique it is likely that there would be an added benefit on top of standard therapies such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta blockers; but this has yet to be tested. Another question is whether this therapy would work if the rTIMP-3 were delivered later after the occlusion. In the present paper it appears that the therapy was given directly after or soon after coronary occlusion. Therefore an acute reduction of infarct size cannot be ruled out, especially since the 4th figure (19) shows an early benefit of therapy on ejection fraction by day one. So it would be useful to repeat this study, giving the injections a few days after the coronary occlusions when infarct size has already been established. It would also be interesting to repeat the study in which therapy is given directly after coronary occlusion but infarct size is assessed by triphenyltetrazolium chloride within 24 hours. That would help establish whether therapy is acutely reducing infarct size or whether it is working primarily on the healing phase of infarction. Finally, the model used in this study was a permanent ligation model and as a first step to determining whether an agent can reduce left ventricular remodeling, this model does make intrinsic sense. However, at some time it would be useful to know if this therapy worked in a reperfused infarct model, as that is the current standard of therapy for the treatment of myocardial infarctions.

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