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Infarct Restraint to Limit Adverse Ventricular Remodeling

Robert C. Gorman,

Department of Surgery, University of Pennsylvania, Philadelphia, PA, USA

Gorman Cardiovascular Research Group, Glenolden Research Laboratory, University of Pennsylvania, 500 S. Ridgeway Avenue, Glenolden, PA 19036, USA

Benjamin M. Jackson,

Department of Surgery, University of Pennsylvania, Philadelphia, PA, USA

Gorman Cardiovascular Research Group, Glenolden Research Laboratory, University of Pennsylvania, 500 S. Ridgeway Avenue, Glenolden, PA 19036, USA

Jason A. Burdick, and

Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, USA

Joseph H. Gorman

Department of Surgery, University of Pennsylvania, Philadelphia, PA, USA

Gorman Cardiovascular Research Group, Glenolden Research Laboratory, University of Pennsylvania, 500 S. Ridgeway Avenue, Glenolden, PA 19036, USA

Abstract

The left ventricular response to a myocardial infarction is a complex biomechanical process that is only beginning to be understood. Infarct expansion (stretching) is an immediate and progressive phenomenon that is known to initiate and sustain the ventricular dilatation and global loss of contractile function that leads to symptomatic heart failure. Limitation of infarct expansion has, therefore, been identified as a potential therapeutic goal that could reduce the morbidity and cost associated with adverse infarction-induced ventricular remodeling and the symptomatic heart failure that results from it. This review will present experimental work that demonstrates the central importance of infarct expansion to the remodeling process as well as proof-of-concept studies that establish the efficacy of early mechanical infarct restraint for limiting ventricular remodeling after myocardial infarction (MI). Ventricular restraint with polymeric mesh materials (wraps) placed early after MI will be discussed. Data supporting the use of injected acellular biomaterials to alter infarct material properties (stiffness) and geometry (thickness) will also be presented. This approach has been shown to be effective in our laboratory and others in limiting post-infarction remodeling and represents a potential means for limiting infarct expansion early after MI via minimally invasive catheter-based technology.

Keywords

Myocardial infarction; Ventricular remodeling; Heart failure; Biomaterials

Introduction

Recent studies of the biomechanical response of the left ventricle (LV) to myocardial infarction (MI) have identified infarct expansion (i.e., stretching) as an important phenomenon that both initiates and sustains a progressive pathologic process that ultimately results in LV dilatation, loss of global contractile function, symptomatic heart failure, and death. This maladaptive response is termed infarction-induced ventricular remodeling and is a complex process that is, in its initial phase, an almost completely a mechanical problem manifest by abnormal myocardial stress patterns; however, with time these abnormal stress distributions lead to inherent biologic changes in the myocardium that become difficult to reverse by any means once established [1–7].

Awareness of the progressive nature of MI-induced LV remodeling and the relatively poor outcomes achieved with therapy for end-stage heart failure has led to increasing interest in developing early post-MI therapies intended to limit adverse remodeling [6]. For over a decade, researchers have investigated the possibility of cell transplantation to repair hearts damaged by MI [8,9]. More recently, the emerging fields of tissue engineering and material science have also begun to provide potential treatments. There are currently three general therapeutic approaches that are under development to limit adverse remodeling after MI. The first involves cell therapy and in vitro engineered cardiac tissues that are intended to be introduced early after infarction with the goal of regenerating/replacing myocardium lost to infarction. While this approach is conceptually attractive and has demonstrated efficacy in small animal models, the therapeutic mechanism remains unclear. To date, the generation of integrated and functional new myocardium has not been documented in large animals or humans. The next approach involves LV restraint with polymeric meshed materials (wraps) placed early after MI. This approach has been shown to be highly effective in limiting remodeling by reducing infarct expansion in clinically relevant large animal models of MI. The clinical applicability of this method is likely limited due the need for thoracotomy in the early post-MI period. The final approach entails injecting acellular biomaterials to alter infarct material properties (stiffness) and geometry (thickness). This approach has shown efficacy in our laboratory and others in limiting post-MI remodeling and represents a potential means for limiting infarct expansion early after MI via catheter-based technology [10].

The goal of this brief review is to summarize compelling proof-of-concept data that support the therapeutic value of early infarct restraint for limiting adverse LV remodeling. Additionally, the potential for materials amenable to percutaneous catheter-based delivery to achieve therapeutic infarct modification (stiffening and thickening) will also be presented.

The Problem

Each year, 935,000 Americans experience a myocardial infarction. Advances in the treatment of acute MI have reduced pre-hospital and in-hospital mortality to less than 9%. In spite of this success (or because of it), MI has become a major cause of heart failure. The most recent data indicate that 5,800,000 Americans suffer from heart failure with a yearly incidence of 670,000 new cases and a yearly mortality of over 280,000. Additionally, greater than 1 million hospitalizations occur each year to treat heart failure at a cost of nearly 40 billion dollars [11].

Currently, the optimal management of acute MI is predicated on expeditious reperfusion therapy followed by long-term pharmacologic treatment with ACE inhibition and beta adrenergic blockade [12,13]. In spite of widespread acceptance of this therapeutic strategy, the incidence and treatment costs for heart failure continue to be high. An alternative or adjunctive therapy designed to limit the MI-induced progression to heart failure would likely

improve longevity and reduce healthcare costs. The development of such a treatment is dependent on a clear understanding of the mechanism that causes a heart that is initially compensated in the early post-MI period to progressively dilate, lose contractile function and, ultimately, fail.

The Mechanism of MI-Induced LV Remodeling: Infarct Expansion and Borderzone Extension

Left ventricular remodeling is manifest clinically by changes in size, shape, and function of the heart as a result of a localized myocardial injury [14]. Extensive work by our group and others has identified infarct expansion as the central phenomenon that is responsible for initiating and sustaining pathologic LV remodeling after MI [5]. Immediately after the onset of ischemia, the infarct region ceases to contract and is subjected to the hemodynamic load produced by the remainder of the ventricle. This abnormal loading results in thinning and stretching of the infarct (i.e., expansion) as well as increased mechanical stress in the perfused borderzone region adjacent to the infarct (Fig. 1).

Using an ovine infarct model and sonomicrometry array imaging, our laboratory has demonstrated that early infarct expansion is associated with progressive loss of contractile function in perfused myocardium adjacent to the infarct. We have also shown that this dysfunctional borderzone becomes more hypocontractile and progresses to involve additional perfused myocardium as remodeling continues and heart failure develops. Contractile dysfunction and geometric distortion (stretching and wall thinning) within the borderzone can be so extensive that perfused borderzone myocardium cannot be distinguished from infarct without a definitive assessment of perfusion status (Fig. 2)[5].

Progressive enlargement of borderzone myocardium following a transmural myocardial infarction has also been identified clinically. Narula and colleagues, using a novel four-stage single-photon emission computed tomographic imaging protocol in patients with ischemic, dilated cardiomyopathy demonstrated that over 50% of the severely dysfunctional myocardium segments had normal blood flow. These data suggest that the extension of borderzone myocardium described experimentally in our laboratory contributes significantly to the development of infarction-induced cardiomyopathy in patients. Narula proposed that this hypocontractile but normally perfused myocardium be called “remodeled myocardium” [15].

We have used contrast-enhanced echocardiography to estimate borderzone stress after coronary occlusion in an ovine experimental infarct model. This work demonstrated that geometric changes consistent with increased circumferential wall stress in the borderzone occurred immediately after the onset of ischemia and was associated with decreased wall thickening in this region of the myocardium. Given its near instantaneous manifestation, we concluded that the early contractile dysfunction seen in this borderzone region is likely due exclusively to a mechanical disadvantage associated with increased regional stress [16].

Guccione and colleagues using an elegant MRI-based finite element model of the chronically remodeled post-MI ovine LV have demonstrated that elevated wall stress levels alone account for neither the severity nor the extent of contractile dysfunction that occur as a result of chronic post-infarction remodeling. These authors used a three-dimensional finite element model derived from multiple short- and long-axis MRI slices of the sheep LV after anteroapical aneurysm formation (8 weeks after MI) to predict mid-wall fiber strain and stress throughout the LV wall during systole while active stress development (contractility) in the borderzone region and infarct stiffness was varied. When the infarct region in this model was assigned realistic material properties, borderzone contractility had to be reduced to 50% of that in regions remote from the infarction in order to reproduce stretching of

borderzone fibers during isovolumic systole that were measured with MRI. Stresses in the anterior and posterior borderzone regions in these chronically remodeled hearts were increased by 50% and 65%, respectively, relative to remote regions. These authors reasonably concluded that in the chronically remodeled heart, there must be additional intrinsic alterations in the remodeled myocardium that inhibit contractile function beyond that which can be attributed to increased regional stress alone [17].

The nature of these inherent myocardial changes is a subject of ongoing research. Recent data from human and animal studies indicate that myocyte apoptosis is an important contributor to the contractile dysfunction seen in remodeled myocardium [18]. Infarction-induced remodeling also leads to changes in the structure of the myocardial interstitium. The extracellular matrix (ECM) is a highly organized collagen scaffolding that maintains ventricular geometry and acts to harness the contractile force of myocytes. This collagen network is maintained by a precise balance in expression and activity of two groups of enzymes: matrix metalloproteinases (MMP) and tissue inhibitors of matrix metalloproteinases (TIMP). Experimental studies have demonstrated that the balance between MMP and TIMP activity is profoundly disturbed in remodeled myocardium. This imbalance leads to disruption of the normal ECM structure and is associated with progressive fibrosis and ventricular dilatation [19].

The reversibility of myocardial pathology found in the chronically remodeled heart has not been determined; however, some conclusions can be surmised from the long and sobering clinical experience with surgical interventions for established heart failure. Aggressive operations designed to reshape the LV and reduce wall stress have repeatedly failed to alter clinical outcomes which strongly suggests that the inherent myocardial changes associated with LV remodeling are difficult if not impossible to reverse once fully established [20].

A thorough analysis of the available clinical and laboratory data establishes the following important facts:

1. Infarct expansion occurs immediately after MI and is progressive
2. Increased borderzone stress occurs immediately after MI, is progressive in severity and expansive in scope (i.e., involves more and more myocardium over time)
3. Increased borderzone stress leads to inherent changes in the remodeled myocardium that further exacerbates contractile dysfunction beyond what can be explained by increase stress levels alone.
4. Once these inherent myocardial changes occur, they are difficult to reverse even by aggressive surgical restructuring of the LV.

Infarct Material Properties: Why Does the Infarct Stretch?

Modeling studies have suggested that the degree of systolic impairment, borderzone stress, and global remodeling should all be directly related to infarct compliance (inversely related to infarct stiffness) [21]. The infarct expansion that occurs concomitantly with the onset of ischemia is readily explained by loss of active contraction which results in infarct region. The infarct maintains near-normal passive diastolic material properties as the remainder of the LV contracts and cavity pressure rises. Over the course of hours, days, and weeks, a complex wound healing process occurs in the infarct region which affects its material properties. It is these material properties that determine the extent of infarct expansion and, therefore, the fate of the entire LV. In spite of the central role that infarct material properties play in the remodeling process, little quantitative data are available on infarct stiffness and how it changes with time. Until recently, it had been widely believed that since infarct collagen content increases with time, that infarct stiffness should also progressively increase.

This hypothesis is, however, inconsistent with the well-described clinical phenomenon of infarction-induced LV remodeling. Gupta and colleagues used biaxial force-extension testing to assess material properties of sheep infarct tissue over a 6-week period. These authors demonstrated that the infarct became more compliant between 2 and 6 weeks in spite of increasing collagen content as the ventricle progressively dilated. They also showed that infarct material properties exhibited substantial anisotropic material properties (less stiffness in the longitudinal direction) [22]. This progressive loss of stiffness during remodeling may seem counterintuitive, but it is thoroughly consistent with the LV remodeling process that is seen clinically and in experimental animal infarct models.

Infarct Expansion as a Therapeutic Target: Proof of Concept

To assess the potential therapeutic efficacy of limiting infarct expansion on LV remodeling, we studied the effect of a LV wrapping with Mersilene® mesh or infarct stiffening with Marlex® mesh using both anteroapical and posterobasal ovine infarct models that have been established and standardized in our laboratory [23,24]. Both models result in infarcts of between 20% and 25% of the LV mass; the anteroapical infarct results in apical aneurysm formation and the posterobasal infarct is associated with ischemic mitral regurgitation. Intervention was performed 7 to 14 days *before* infarction. Our intent in these idealized experiments was to test a “best case scenario” to prove the concept that infarct restraint limits adverse LV remodeling. Animals with each infarct received either no treatment, infarct stiffening with a localized Marlex® mesh patch sutured over the area of the intended infarct or LV wrapping (RV not covered) with Mersilene® mesh. Quantitative echocardiography was performed serially to evaluate the extent of LV remodeling. Control animals with either infarct experienced adverse remodeling. However both early infarct stiffening (Marlex® patch) prophylactic LV wrapping (with Mersilene®) significantly improved remodeling. Additionally, LV wrapping was superior to infarct stiffening alone in limiting adverse LV remodeling.

These early proof-of-concept studies were followed by an experiment in which the infarct was restrained at a more clinically relevant time point (1 week after MI). In this experiment, we used an ovine anterobasal infarct model and high spatial and temporal resolution cardiac MRI to quantify total and infarcted LV epicardial surface area at baseline and 1 week and 12 weeks after infarction in 10 animals. Borderzone radial systolic strain (i.e., wall thickening) and temporal systolic strain propagation (i.e., time course of wall thickening) were also determined. Titanium markers (1 mm) were sutured around the infarct region to allow delineation of the infarcts size via MRI. Five animals were randomly assigned to treatment with left ventricular restraint (Acorn CSD®) 1 week after infarction. Five animals were untreated controls. Total left ventricular surface area was measured by importing the end-diastolic MRI-derived epicardial contours into custom software, which created a three-dimensional surface from the MRI contours. Infarct area was calculated. Borderzone radial and circumferential strains during systole were also assessed using the optical flow mapping techniques. The infarct area 1 week after infarction was $1,177 \pm 386 \text{ mm}^2$ in the control group and $1,124 \pm 427 \text{ mm}^2$ in the CSD group. After 12 weeks, infarct area was $3,666 \pm 1,013 \text{ mm}^2$ in the control group and $1,227 \pm 301 \text{ mm}^2$ in the CSD group (Fig. 3). Borderzone systolic radial strain decreased from $12.6 \pm 0.77\%$ to $3.6 \pm 0.3\%$ after infarction in the control group and $13.7 \pm 0.87\%$ to $4.7 \pm 0.3\%$ in the cardiac support device group. At 12 weeks after infarction, radial strain was $3.4 \pm 0.5\%$ in the control group and $6.7 \pm 0.4\%$ in the cardiac support device group. Systolic strain propagation was also improved in the CSD group. This study provided further evidence that early post-infarction left ventricular restraint limits infarct expansion and improves borderzone contractile function [25,26].

The Theoretic Benefit of Direct Infarct Modification

The work performed in our laboratory strongly supports the prevention infarct expansion as an important therapeutic goal intended to limit MI-induced LV remodeling; however, the use of external restraint devices in the form of mesh jackets and patches is never likely to achieve widespread clinical application because of the invasive surgical procedures that would be required in the early post-MI period to place them. Given this clinical reality, our group and others have begun to explore and develop the use of novel liquid biomaterials to modify infarct material characteristics so as to limit or prevent progressive infarct expansion. The use of such materials holds the potential for percutaneous, catheter-based approaches for beneficially altering the post-MI LV remodeling process.

Using modeling algorithms, our group and others have established the theoretical basis for direct infarct modification as a treatment strategy. To assess how infarct compliance affects LV size and function after myocardial infarction, we employed a closed-loop lumped parameter model of the ovine cardiovascular system that was developed to study the effect of infarct size and compliance on cardiovascular function. The time-varying LV function was partitioned into infarct and non-infarct regions where the parameters of each could be adjusted separately. In addition, the model incorporated an adaptive compensatory mechanism to maintain stroke volume by varying the total blood volume. For the pre-infarction heart, the model produced pressure, volume, and function results that were consistent with normal values for sheep. Likewise, when infarcts of progressively larger size (5% to 25%) were introduced and stroke volume adaptation was permitted, the model produced pressure, volume, and function results that were consistent with post-MI values measured experimentally in sheep. Finally, infarct size was held at 20% as infarct compliance decreased from 7 ml/mmHg to 1 ml/mmHg. Stiffening of the infarct resulted in reduced LV end diastolic volume (200 ml to 60 ml), increased ejection fraction (10% to 30%), and reduced LV end diastolic pressure (14 mmHg to 5 mmHg). Estimated LV oxygen consumption was also improved in the stiffer infarcts. Stiffer infarcts were associated with less LV dilatation, reduced filling pressures, and better global LV function [27].

Wall and colleagues [28] also hypothesized that implanted biomaterials may result in beneficial alterations in ventricular mechanics. Using the Guccione finite element model of the ovine left ventricle with an anteroapical infarct, these investigators modeled the short-term effect of injecting material into the left ventricle to regionally augment wall volume. The model's mesh and regional material properties were modified to simulate expected changes. Three sets of simulations were run: (1) single injection to the anterior borderzone, (2) therapeutic multiple borderzone injections, and (3) injection of material to the infarct region. Results indicated that injections to the borderzone decrease end-systolic fiber stress proportionally to the fractional volume added, with stiffer materials improving this attenuation. Small changes in wall volume (<4.5%) reduced elevated borderzone fiber stresses from mean end-systolic levels of 28.2 kPa (control) to 23.3 kPa (treatment). Infarct injection improved ejection fraction and the stroke volume/end-diastolic volume relationship.

The Use of Biomaterials: A Step Towards Clinical Relevance

We tested the hypothesis that injection of a dermal filler agent (marketed to treat facial wrinkles) into a sheep anteroapical infarct 3 h after MI would lead to improved global LV function and attenuate long-term LV remodeling. We further hypothesized that the material would increase infarct thickness and stiffness. We selected Radiesse® because it is the most durable dermal filler and has the largest elastic modulus (6 kPa; i.e., is more stiff) of the existing dermal filler products. Radiesse is calcium hydroxyapatite (CaHA) microsphere (25–45 µm) gel suspension that is composed of CaHA (30%) suspended in a gel carrier

(70%) that consists of sodium carboxymethylcellulose, glycerin, and water. Twenty-one sheep had a standard anteroapical infarct. Seven were untreated controls; seven had injection of 1 ml of Radiesse into the infarct in 20 evenly divided doses and seven had injection of 3 ml of Radiesse (Fig. 4). 2D dobutamine stress echocardiography was performed at 8 weeks after MI. Infarct thickness was directly measured in the post-mortem specimen. Infarct stiffness was measured by a biaxial force-extension method. Infarct thickness was 2.1 ± 0.3 mm, 4.0 ± 0.3 mm, and 5.9 ± 0.6 mm in the control, 1 ml, and 3 ml groups, respectively (Fig. 4). Infarct stiffness was progressively increased with increasing Radiesse® dose. The 3 ml Radiesse group had a highly significant improvement in global function, LV remodeling, and response to dobutamine (Fig. 5) [29].

Other groups have recently presented data that has demonstrated the potential of injectable materials to favorably affect post-MI LV remodeling [30–35]; only a few groups [29,34,35] have evaluated the impact of acellular intramyocardial injections in large animal models of MI. Furthermore, the influence of specific properties of the injectate on the associated LV remodeling response has not been explored experimentally and is not well understood. This is partially due to the difficulty in developing materials that can be used to systematically investigate the influence of one property (e.g., mechanics) without altering other potentially confounding parameters (e.g., degradation). In an attempt to address this limitation, we studied injectable hyaluronic acid (MeHA) hydrogels that have tunable mechanics and gelation behavior. Specifically, two MeHA formulations that exhibit similar degradation and tissue distribution upon injection, yet have differential moduli (~ 8 versus ~ 43 kPa), were injected into a clinically relevant ovine MI model to evaluate the effect of intramyocardial hydrogel injection on the remodeling response based on hydrogel mechanics. Treatment with both hydrogels significantly increased the wall thickness in the infarct regions compared to the control infarct. However, only the higher modulus (MeHA High) treatment group had a statistically smaller infarct area compared to the control infarct group. Moreover, reductions in end-diastolic and end-systolic volumes were observed for the MeHA High group. This group also tended to have better functional outcomes (cardiac output and ejection fraction) compared to the low modulus (MeHA Low) and control infarct groups. This study produced fundamental information that represents an initial step towards the rational design of therapeutic materials for treatment of MI [36].

Summary

The left ventricular response to a myocardial infarction is a complex biomechanical process that is only beginning to be understood. Infarct expansion is an immediate and progressive phenomenon that initiates and sustains the ventricular dilatation and global loss of contractile function that leads to symptomatic heart failure. Limitation of infarct expansion is, therefore, a viable therapeutic objective that may reduce the morbidity and cost associated with adverse infarction-induced ventricular remodeling and the symptomatic heart failure that results from it. The data presented in this review has demonstrated the central importance of infarct expansion to the remodeling process. Proof-of-concept studies have established the efficacy of early mechanical infarct restraint for limiting ventricular remodeling after myocardial infarction. Ventricular restraint with polymeric mesh materials and wraps placed early after MI are effective; however, the invasive surgical means that are required for placement make their widespread clinical acceptance unlikely. The use of injected acellular biomaterials to alter infarct material properties and geometry has also been shown to be effective for positively influencing the remodeling process and represents a potential means for limiting infarct expansion early after MI via minimally invasive catheter-based technology.

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Fig. 1. Infarction-induced left ventricular remodeling schematic—progressive infarct expansion (stretching) initiates and sustains the remodeling process leading ventricular dilation, global loss of contractile function, and symptomatic heart failure

Fig. 2.

Infarct expansion and LV remodeling—graphs depicting the relationship between the geometric change (expansion) and functional change (contractile function) for each of 30 intertransducer segments in the left ventricular (LV) myocardium: *red symbols* represent segments located within the anatomical infarction; *green symbols* represent segments located outside the infarction in normally perfused myocardium. No graph is shown for the pre-infarction case because only *changes* in chord length and contractile function are plotted; prior to infarction all chords would lie at the origin. The *horizontal line* $y=0$ represents a segment of myocardium which has exactly the same fractional contraction as it had at the baseline study; segments which fall between $y=0$ and $y=-100\%$ are hypocontractile relative to baseline; segments falling below $y=-100\%$ demonstrate systolic dyskinesia. Displacement along the *x-axis* represents lengthening of a chord. Below each graph is the corresponding array of sonomicrometry transducers, as seen through a left thoracotomy. *Dashed lines* indicate segments that fall below the line $y=0$. The *dashed green lines* represent hypocontractile but perfused myocardium (borderzone myocardium) and *dashed red lines* represent infarcted myocardium. Note the progressive numerical increase and location of the hypocontractile dashed segments, demonstrating both the focal dilatation of the anteroapical infarction and the global expansion of the ventricle over 8 weeks. The lone transducer outside the array represents a crystal placed on the aorta for purposes of geometric orientation

Fig. 3.

Prevention of infarct expansion with ventricular restraint—three-dimensional epicardial surface model for representative control (**a**) and Acorn CSD® treated (**b**) animals 12 weeks after infarction. Models were generated from MRI in which detectable markers used to delineate the infarct from perfused myocardium. *Red triangles* indicate the area of perfused myocardium while the *blue triangles* are the area bounded by the markers and represent infarcted myocardium. Note the difference in overall LV size and infarct area between the control animal and CSD treated animal

Fig. 4. Radiesse® injection to limit infarct expansion—**a** sheep heart as viewed through a left thoracotomy after anteroapical infarction. **b** Same heart after administration of 3 ml of calcium hydroxyapatite microsphere gel suspension (Radiesse®) in 20 equal injections 3 h after coronary artery occlusion. The *light blue line* is the demarcation between infarct and perfused myocardium. **c** Infarct thickness 8 weeks after MI in an untreated control animal. **d** Infarct thickness 8 weeks after MI in an animal treated with 3 ml of Radiesse®. The sections of myocardium shown were excised from base to apex on the anterior wall of the left ventricle

Fig. 5.

Stress echocardiography after infarct modification—dobutamine stress echocardiography data for untreated sheep 8 weeks after anteroapical infarct, infarcted sheep treated with 3 cc of Radiesse® also 8 weeks after MI and normal (uninfarcted) sheep. **a** LV systolic volume 8 weeks after MI was significantly reduced in the Radiesse® treated animals compared to control. **b** Resting EF was significantly better in the Radiesse® treated animals as was the response to dobutamine