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WHY IS INFARCT EXPANSION SUCH AN ELUSIVE THERAPEUTIC TARGET?

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Abstract

Myocardial infarct expansion has been associated with an increased risk of infarct rupture and progression to heart failure, motivating therapies such as infarct restraint and polymer injection that aim to limit infarct expansion. However, an exhaustive review of quantitative studies of infarct remodeling reveals that only half found chronic in-plane expansion, and many reported in-plane compaction. Using a finite-element model, we demonstrate that the balance between scar stiffening due to collagen accumulation and increased wall stresses due to infarct thinning can produce either expansion or compaction in the pressurized heart – potentially explaining variability in the literature – and that loaded dimensions are much more sensitive to changes in thickness than in stiffness. Our analysis challenges the concept that in-plane expansion is a central feature of post-infarction remodeling; rather, available data suggest that radial thinning is the dominant process during infarct healing and may be an attractive therapeutic target.

Keywords

infarction; remodeling; expansion; mechanics; fibroblast; wound healing

Introduction

Following a myocardial infarction (MI), long-term remodeling of both the damaged infarct region and the remaining viable myocardium are critical determinants of patient outcomes and the risk of progression to post-infarction heart failure [1]. One commonly described feature of this remodeling process is infarct expansion, originally defined as the combination of thinning of the healing infarct in the radial direction and dilation in the circumferential-longitudinal plane (parallel to the epicardium, hereafter referred to as “in-plane”) [2]. Over the decades since its original description, studies have shown that the risk of infarct expansion is greatest in patients with large, transmural, anterior infarcts and that expansion

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is associated with increased risks for rupture and progression to heart failure [3–6]. In the first few hours post-MI, expansion apparently occurs via stretching and permanent rearrangement of damaged myocytes [7,8]. Over the next few weeks, changes in infarct dimensions are determined by a more complicated balance between ongoing tissue remodeling and mechanical loading. Myocytes are degraded and resorbed and myofibroblasts infiltrate the tissue, depositing and remodeling a collagenous scar [9]. The resolution of edema and progressive myocyte resorption both contribute to infarct thinning, while infarct thinning and global left ventricular (LV) dilation both promote in-plane expansion by increasing wall stresses [10]. These pro-expansion forces are opposed by the progressive accumulation of collagen, which increases infarct stiffness, and possibly by active contraction of myofibroblasts within the scar, which may drive in-plane compaction [11–14].

Given the association of infarct expansion with risk for further complications, a number of recently developed therapies are designed to work primarily or partly by limiting infarct expansion. For example, local restraint devices have been sewn to the epicardial surface over the infarct to restrict in-plane dimension increases [15–18], polymeric materials have been injected into scar to increase scar stiffness and/or thickness and thereby resist distension [19], myofibroblasts have been targeted to enhance scar compaction forces [11], and collagen turnover has been pharmacologically modulated in order to increase collagen content and stiffness [20]. While individual studies have reported reduced local or global remodeling or improved LV function, many of these studies have shown surprisingly little benefit, and data from multiple studies of similar interventions often conflict. We hypothesized that some of this variability in the literature was due to differences among animal models in the time course of dimension changes in the damaged region following MI.

Accordingly, we conducted an exhaustive review of studies that quantified thinning, in-plane dimension changes, or other measures of infarct expansion in a range of animal models as well as in patients. To our surprise, we found that only half of studies reported in-plane expansion of healing infarcts beyond the first 24 hours, and many reported in-plane compaction. Furthermore, measurements in unloaded, arrested hearts were less likely to show in-plane expansion. These findings suggested to us that progressive changes in infarct dimensions *in vivo* reflect a dynamic balance between infarct stiffening and increasing wall stresses due to thinning, a concept we tested using a computational model. Our results suggest a reinterpretation of the concept of infarct expansion beyond the first 24 hours, wherein infarct thinning is the central, dominant feature of infarct remodeling while changes in in-plane dimension are variable and secondary to the balance between thinning and stiffening. Such a re-interpretation could provide clearer design goals for novel therapies currently in development for post-MI treatment.

Methods

Literature Review

We searched PubMed for studies containing title/abstract words “infarct” + “expansion” + (“measure” or “dimension” or “size”) + (“serial” or “chronic”), published during the period

1/1/1950 – 7/28/2015. An initial 72 matches plus additional studies referenced within those matches yielded 97 total reports for review. Many were excluded from analysis because they reported only composite measurements from which it was impossible to distinguish changes in infarct thickness from changes in one or more in-plane dimensions (e.g. infarct area measured in a short-axis slice from the LV). The remaining studies reported serial measurements of infarct thickness (13 studies), in-plane dimension (27 studies), or both thickness and in-plane dimension (19 studies). Data from these studies were assimilated and included the following measurements: absolute thickness, thickness relative to remote myocardium, absolute circumferential or longitudinal segment lengths, circumferential segment length relative to LV circumference, infarct-containing segment length defined either using septal bisector or papillary muscle demarcations, and in-plane area. Importantly, some of these studies measured infarct dimensions in arrested, unloaded ventricles, while others measured them *in vivo* or following fixation under load. When unloaded, the infarct was usually identified by histological staining; when loaded, the infarct was usually identified as the akinetic-dyskinetic segment, or by gadolinium-enhanced MRI. From the reported measurements, thickness and in-plane dimension ratios were calculated at each time point relative to the earliest measurement post-MI when assessing acute expansion and relative to the earliest measurement at least 24h post-MI when assessing chronic expansion. Therefore, a relative thickness ratio <1 reflects thinning and >1 reflects thickening, while a relative in-plane ratio <1 reflects in-plane compaction and >1 reflects in-plane expansion.

Contributions of Infarct Stiffening and Thinning to Measured Infarct Dimensions

In order to systematically evaluate the combined effects of different degrees of infarct thinning and stiffening on infarct dimensions measured at end diastole, we constructed a finite-element model (FEM) of the infarcted rat left ventricle and the infarcted dog left ventricle in FEBio [21]. We utilized the geometry of infarcted rat and dog left ventricles 2 days after coronary ligation imaged in our lab using gadolinium-enhanced MRI. The endocardial, epicardial, and infarct outlines were traced, reassembled in 3D-space, and fit in a prolate spheroidal coordinate system using previously published methods [22]. The fit was used to generate the FEM geometry consisting of 8400 elements for the rat and 7600 elements for the dog. Material properties were assumed to follow the neo-Hookean material constitutive relation in Equation 1, with baseline parameters fitted to match LV end-diastolic pressure-volume relationships measured previously by Omens and colleagues in rats [23] and Fomovsky and colleagues in dogs[18]:

$$W = c \left(\tilde{I}_1 - 3 \right) + \frac{1}{2} K (\ln(J))^2 \quad \text{Eq. 1}$$

where W is the strain-energy of the material, c is a stiffness parameter, $\tilde{I}_1$ is the first invariant of the deviatoric right Cauchy-Green deformation tensor, K is the bulk modulus, and J is the Jacobian of the deformation gradient tensor. In order to predict the effects of thinning and stiffening on loaded in-plane dimensions in the FEM, we systematically varied the infarct thickness in the unloaded state from baseline to $0.4 \times$ baseline, while also varying scar material stiffness parameters from baseline to $3 \times$ baseline, then inflated the model ventricle from 0 to a typical end-diastolic pressure (10mmHg for rat, 12mmHg for dog) and

calculated the resulting relative infarct circumferential segment length as the transmural average across 12 elements in the center of the infarct.

Results

Previous Reports Show Both In-Plane Expansion and Compaction in Healing Infarcts

Among the 46 studies we identified that quantified changes in infarct in-plane dimension in mice, rats, dogs, pigs, sheep, baboons, and patients, the 8 that reported measurements over the first 24 hours consistently reported in-plane expansion (Figure 1A) [5,7,24–29]. By contrast, results from the 40 studies that measured dimensions beyond 24 hours were surprisingly diverse: 20 showed significant in-plane expansion [4,30–48], 9 showed significant compaction [9,14,49–55], and 11 showed no significant change in either direction [5,27,56–64] (Figure 1B). Interestingly, nearly all studies that reported in-plane expansion beyond 24 hours measured infarct dimensions while the ventricle was under load, while measurements in unloaded arrested hearts were more likely to show compaction than expansion. This suggested to us that the variability in reported in-plane dimensions could reflect variability in infarct stretching under load, rather than differences in rearrangement of cells or extracellular matrix as originally described for acute expansion; we therefore grouped studies by loading state in subsequent analyses.

Plotting infarct thickness ratio over time, we found that studies consistently show infarcts progressively thinning over the healing time course, regardless of animal model and whether measurements were made in loaded or unloaded configurations (Figure 2A). Analyzing in-plane dimension ratio over time revealed that measurements made in the unloaded state typically show in-plane compaction, while those made in the loaded state show much more variability: modest changes at all times in patients, expansion on average in rats and sheep (particularly at later time points), and a surprisingly wide range of both compaction and expansion in dogs (Figure 2B).

Balance of Stiffening and Thinning Can Account for Variability in End-Diastolic Dimensions

Nearly all the studies that measured dimensions under load made those measurements at end diastole *in vivo* or in hearts fixed at end-diastolic pressure (39 of 49 explicitly stated this). To investigate the effects of infarct stiffening and thinning on in-plane dimensions at end diastole, we built an FEM of infarcted rat and dog ventricles in which we varied unloaded infarct properties and wall thickness, then computed end-diastolic infarct dimensions at typical end-diastolic pressures (10 mmHg for the rat and 12 mmHg for the dog). We found that, over a physiologically plausible range of values, the balance between infarct stiffness and thickness determined whether the infarct appeared to expand or compact in the circumferential direction relative to baseline (Figure 3). Figure 3b shows examples of the effects of stiffening alone or thinning alone in the rat to further illustrate the differences. When stiffened 2.5-fold, the infarct circumferential dimension at end-diastole decreased 16% from 8mm (baseline case) to 6.7mm, a change that would be interpreted as in-plane compaction in a typical *in vivo* study; alternatively, when thinned to 0.6-fold, the end-diastolic circumferential dimension increased 40% from 8mm to 11.2mm, a change that

would be reported as in-plane expansion. Systematically comparing a range of stiffness and thickness combinations showed that about half of the simulated cases would display in-plane infarct expansion and half would display infarct compaction based on dimensions measured at end diastole, consistent with the balance of reports from the literature review presented above (Figure 3c). Interestingly, in-plane stretch during simulated filling was substantially more sensitive to changes in thickness than to changes in stiffness; therapeutic implications of this finding are discussed below. Compared to the rat model, the same degree of infarct stiffening had a slightly smaller effect on end-diastolic dimensions in the dog model, but all other trends were similar (Figure 3d–e). We note that some infarcts have been reported to be structurally and mechanically anisotropic [65–67], in which case in-plane stretching in the circumferential and longitudinal directions could differ; however, deformation in either direction would still reflect the balance between stiffness in that direction and wall thinning.

Discussion

Infarct expansion is a widely recognized feature of post-infarction remodeling that is associated with worse clinical outcomes and has been targeted by a number of recently developed therapies. Yet a careful review of quantitative data in the literature reveals that beyond the first 24 hours, only 20 of 40 studies reported statistically significant in-plane expansion, and sheep were the only species whose infarcts reliably expanded. In addition to highlighting the prevalence of infarct compaction, our literature review clearly shows how strongly apparent infarct remodeling depends on the loading state in which the measurements are made. When infarct dimensions are measured at diastolic pressures, chronic expansion is reported 60% of the time (20/34 studies), but measurements in unloaded arrested hearts show expansion only 30% of the time (3/10). Using a simple finite-element model, we showed that the competing balance between scar stiffening and thinning can give rise to either apparent compaction or expansion under load, even when infarct in-plane dimensions remain unchanged in the unloaded state, an observation that could explain much of the variability in literature reports.

There are three important therapeutic implications of the data reviewed here. First, the wide range of in-plane dimension changes that occurs *in vivo* across different animal models may explain variability in the reported success of local biomaterial-based and surgical strategies in limiting post-infarction remodeling. Broadly, whole-ventricle restraints have consistently reduced ventricular dilation post-MI; however, localized epicardial patches and localized polymer injections that support only the infarcted region have produced more variable results (Table 1) [15,16,68–81]. More specifically, of the few local support studies that report in-plane scar dimensions, only three significantly decreased infarct expansion [69,76,80], while just as many produced no change [75,80] or even increased in-plane expansion [74]. We suggest that this disparity in reported effects of local vs. global support is at least partly due to the fact that infarcts don't always expand even when untreated; therefore, local support will only sometimes produce a change in dimensions.

Second, our finite-element model results suggest that increasing scar stiffness or increasing scar thickness can both limit in-plane stretch of the infarct region, but that scar thickness might be a more productive target than scar stiffness since much smaller changes in

thickness are needed to achieve a given reduction in dimension (Figure 3). For example, starting at the center of Figure 3C (thickness = 0.7× and stiffness = 2×), to completely normalize end-diastolic circumferential dimensions would require a 19% increase in stiffness but only a 5% increase in thickness. This high sensitivity to thickness is consistent with an earlier computational study by Wall, and with several studies that have reported reduced LV dilation following interventions that made infarcts thicker but also more compliant [70,82,83]. Indeed, out of 15 interventions listed in Table 1 that significantly increased thickness, 10 led to either decreased cavity volume or improved ejection fraction or fractional shortening. On the other hand, there is very limited data on the efficacy of increasing infarct stiffness using polymer injectables. Only two of nine studies listed in Table 1 measured tissue properties following treatment. Mukherjee and colleagues reported no change in the tensile modulus of pig infarcts injected with fibrin-alginate as measured by pressure-strain curves in intact ventricles [76]. Ifkovitz and colleagues also found no significant change in the tensile modulus of sheep infarcts injected with a methacrylated hyaluronic acid as measured by ex vivo tensile testing of infarct tissue, but they did show a significant increase in compressive modulus [80].

A final important implication of this analysis is that the prevalence of infarct compaction suggests that intrinsic compaction mechanism(s) exist within the scar, which if better understood could potentially be harnessed for therapeutic reduction of infarct size. Consistent with this hypothesis, Laeremans et al. & Barandon et al. modulated Wnt/Frizzled signaling in order to increase fibroblast density in mouse infarcts in an attempt to enhance cell-mediated compaction of the scar; these treatments increased scar thickness and reduced scar area, in spite of decreased scar collagen content [11,84]. It is worth highlighting that while therapies that aim to restrain in-plane expansion will only be beneficial in cases where the baseline infarct is expanding, therapeutically enhancing infarct compaction may potentially show benefit regardless of whether the baseline infarct is expanding or compacting on its own.

One limitation of this review is that the infarct dimension changes reported in Figures 1 & 2 were assimilated from studies that reported a variety of infarct measurements (absolute circumferential segment length, circumferential segment relative to whole ventricle, infarct-containing segment from papillary to papillary, and others). Though we report values normalized within each study, some of these measurements are confounded by borderzone or remote remodeling. Another limitation is that studies that met our inclusion criteria of reporting quantitative measures of thickness and/or in-plane dimension at multiple time points after infarction were not evenly distributed in time or among species. Broadly, studies from the 1970s and 1980s were much more likely to report quantitative measures than more recent studies, and studies in some animal models – particularly dogs – were more likely to report quantitative measures than studies in humans. For example, although our initial PubMed search identified 21 studies in patients, only 9 of these reported quantitative in-plane measures and only one of those studies was published after 1996. Additionally, we should note that since we normalized chronic infarct dimensions to the first measurement taken at least 24h post-MI, it is possible that observed compaction may partly be due to edema resolution. However, it is doubtful that edema resolution would account for progressive compaction beyond 4 weeks as was seen in numerous studies (Figure 2). A

broader limitation of the analysis presented here is that it focuses narrowly on infarct expansion – how frequently it occurs, and why designing therapies that prevent it has proven more difficult than originally expected. How geometric remodeling in the infarct affects remodeling in the remaining non-infarcted myocardium and ultimately modulates the risk of post-infarction heart failure remains an important topic of study. Accordingly, even approaches reviewed in Table 1 that effectively altered in-plane remodeling did not necessarily limit global remodeling or improve LV ejection fraction.

In summary, a comprehensive review of quantitative data available in the literature challenges the concept that in-plane infarct expansion is a central feature of post-infarction remodeling. Rather, available data suggest that radial thinning is the dominant process during infarct healing and may represent an attractive therapeutic target. In addition to preventing infarct thinning, promoting or enhancing infarct compaction may be an under-appreciated therapeutic opportunity.

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Abbreviations

MI	myocardial infarction
LV	left ventricle
FEM	finite element model

References

- [1]. Sharpe N. Ventricular remodeling following myocardial infarction. *The American Journal of Cardiology*. 1992; 70:20–6.
- [2]. Hutchins GM, Bulkley BH. Infarct expansion versus extension: two different complications of acute myocardial infarction. *The American Journal of Cardiology*. 1978; 41:1127–32. [PubMed: 665522]
- [3]. Schuster EH, Bulkley BH. Expansion of transmural myocardial infarction: a pathophysiologic factor in cardiac rupture. *Circulation*. 1979; 60:1532–8. [PubMed: 498481]
- [4]. Eaton LW, Weiss JL, Bulkley BH, Garrison JB, Weisfeldt ML. Regional cardiac dilatation after acute myocardial infarction: recognition by two-dimensional echocardiography. *The New England Journal of Medicine*. 1979; 300:57–62. [PubMed: 758578]
- [5]. Erlebacher JA, Weiss JL, Weisfeldt ML, Bulkley BH. Early dilation of the infarcted segment in acute transmural myocardial infarction: role of infarct expansion in acute left ventricular enlargement. *Journal of the American College of Cardiology*. 1984; 4:201–8. [PubMed: 6234343]
- [6]. Pirolo JS, Hutchins GM, Moore GW. Infarct expansion: Pathologic analysis of 204 patients with a single myocardial infarct. *Journal of the American College of Cardiology*. 1986; 7:349–54. American College of Cardiology Foundation. [PubMed: 2935567]
- [7]. Weisman HF, Bush DE, Mannisi JA, Weisfeldt ML, Healy B. Cellular mechanisms of myocardial infarct expansion. *Circulation*. 1988; 78:186–201. [PubMed: 2968197]

- [8]. Olivetti G, Capasso JM, Sonnenblick EH, Anversa P. Side-to-side slippage of myocytes participates in ventricular wall remodeling acutely after myocardial infarction in rats. *Circulation Research*. 1990; 67:23–34. [PubMed: 2364493]
- [9]. Fishbein MC, Maclean D, Maroko PR. Experimental myocardial infarction in the rat: qualitative and quantitative changes during pathologic evolution. *The American Journal of Pathology*. 1978; 90:57–70. [PubMed: 619696]
- [10]. Holmes JW, Borg TK, Covell JW. Structure and mechanics of healing myocardial infarcts. *Annual Review of Biomedical Engineering*. 2005; 7:223–53.
- [11]. Laeremans H, Hackeng TM, van Zandvoort MAMJ, Thijssen VLJL, Janssen BJA, Ottenheijm HCJ, et al. Blocking of frizzled signaling with a homologous peptide fragment of wnt3a/wnt5a reduces infarct expansion and prevents the development of heart failure after myocardial infarction. *Circulation*. 2011; 124:1626–35. [PubMed: 21931076]
- [12]. Van den Borne SWM, van de Schans V. a M. Strzelecka AE, Vervoort-Peters HTM, Lijnen PM, Cleutjens JPM, et al. Mouse strain determines the outcome of wound healing after myocardial infarction. *Cardiovascular Research*. 2009; 84:273–82. [PubMed: 19542177]
- [13]. Fomovsky GM, Holmes JW. Evolution of scar structure, mechanics, and ventricular function after myocardial infarction in the rat. *American Journal of Physiology Heart and Circulatory Physiology*. 2010; 298:H221–8. [PubMed: 19897714]
- [14]. Holmes JW, Yamashita H, Waldman LK, Covell JW. Scar remodeling and transmural deformation after infarction in the pig. *Circulation*. 1994; 90:411–20. [PubMed: 8026026]
- [15]. Clarke, SA.; Ghanta, RK.; Ailawadi, G.; Holmes, JW. *Cardiac Restraint and Support Following Myocardial Infarction*. Springer Berlin Heidelberg; 2013. p. 1-38.
- [16]. Gorman RC, Jackson BM, Burdick JA, Gorman JH. Infarct restraint to limit adverse ventricular remodeling. *Journal of Cardiovascular Translational Research*. 2011; 4:73–81. [PubMed: 21161462]
- [17]. Ghanta RK, Lee LS, Umakanthan R, Laurence RG, Fox JA, Bolman RM, et al. Real-time adjustment of ventricular restraint therapy in heart failure. *European Journal of Cardio-Thoracic Surgery : Official Journal of the European Association for Cardio-Thoracic Surgery*. 2008; 34:1136–40. [PubMed: 18715793]
- [18]. Fomovsky GM, Clark SA, Parker KM, Ailawadi G, Holmes JW. Anisotropic reinforcement of acute anteroapical infarcts improves pump function. *Circulation Heart Failure*. 2012; 5:515–22. [PubMed: 22665716]
- [19]. Rane, A. a; Christman, KL. Biomaterials for the treatment of myocardial infarction: a 5-year update. *Journal of the American College of Cardiology*. 2011; 58:2615–29. Elsevier Inc. [PubMed: 22152947]
- [20]. Jugdutt BI. Remodeling of the myocardium and potential targets in the collagen degradation and synthesis pathways. *Current Drug Targets Cardiovascular & Haematological Disorders*. 2003; 3:1–30. [PubMed: 12769643]
- [21]. Maas SA, Ellis BJ, Ateshian GA, Weiss JA. FEBio: finite elements for biomechanics. *Journal of Biomechanical Engineering*. 2012; 134:011005. [PubMed: 22482660]
- [22]. Herz SL, Ingrassia CM, Homma S, Costa KD, Holmes JW. Parameterization of left ventricular wall motion for detection of regional ischemia. *Annals of Biomedical Engineering*. 2005; 33:912–9. [PubMed: 16060531]
- [23]. Omens JH, MacKenna D. a, McCulloch a D. Measurement of strain and analysis of stress in resting rat left ventricular myocardium. *Journal of Biomechanics*. 1993; 26:665–76. [PubMed: 8514812]
- [24]. Vokonas PS, Pirzada F, Hood WB. Experimental myocardial infarction: XII. Dynamic changes in segmental mechanical behavior of infarcted and non-infarcted myocardium. *The American Journal of Cardiology*. 1976; 37:853–9. [PubMed: 1266750]
- [25]. Lew WY, Chen ZY, Guth B, Covell JW. Mechanisms of augmented segment shortening in nonischemic areas during acute ischemia of the canine left ventricle. *Circulation Research*. 1985; 56:351–8. [PubMed: 3971509]

- [26]. Mehta PM, Alker KJ, Kloner RA. Functional infarct expansion, left ventricular dilation and isovolumic relaxation time after coronary occlusion: a two-dimensional echocardiographic study. *Journal of the American College of Cardiology*. 1988; 11:630–6. [PubMed: 2963853]
- [27]. Kass DA, Maughan WL, Ciuffo A, Graves W, Healy B, Weisfeldt ML. Disproportionate epicardial dilation after transmural infarction of the canine left ventricle: acute and chronic differences. *Journal of the American College of Cardiology*. 1988; 11:177–85. [PubMed: 3335694]
- [28]. Villarreal FJ, Lew WY, Waldman LK, Covell JW. Transmural myocardial deformation in the ischemic canine left ventricle. *Circulation Research*. 1991; 68:368–81. [PubMed: 1991344]
- [29]. Brown EJ, Swinford RD, Gadde P, Lillis O. Acute effects of delayed reperfusion on myocardial infarct shape and left ventricular volume: a potential mechanism of additional benefits from thrombolytic therapy. *Journal of the American College of Cardiology*. 1991; 17:1641–50. [PubMed: 2033197]
- [30]. Crozatier B, Ross J, Franklin D, Bloor CM, White FC, Tomoike H, et al. Myocardial infarction in the baboon: regional function and the collateral circulation. *The American Journal of Physiology*. 1978; 235:H413–21. [PubMed: 100019]
- [31]. McKay RG, Pfeffer M. a. Pasternak RC, Markis JE, Come PC, Nakao S, et al. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. *Circulation*. 1986; 74:693–702. [PubMed: 3757183]
- [32]. Jugdutt BI, Schwarz-Michorowski BL, Khan MI. Effect of long-term captopril therapy on left ventricular remodeling and function during healing of canine myocardial infarction. *Journal of the American College of Cardiology*. 1992; 19:713–21. [PubMed: 1538033]
- [33]. Nahrendorf M, Wiesmann F, Hiller KH, Hu K, Waller C, Ruff J, et al. Serial cine-magnetic resonance imaging of left ventricular remodeling after myocardial infarction in rats. *Journal of Magnetic Resonance Imaging : JMRI*. 2001; 14:547–55. [PubMed: 11747006]
- [34]. Fieno DS, Hillenbrand HB, Rehwald WG, Harris KR, Decker RS, Parker MA, et al. Infarct resorption, compensatory hypertrophy, and differing patterns of ventricular remodeling following myocardial infarctions of varying size. *Journal of the American College of Cardiology*. 2004; 43:2124–31. [PubMed: 15172424]
- [35]. Blom AS, Pilla JJ, Arkles J, Dougherty L, Ryan LP, Gorman JH, et al. Ventricular restraint prevents infarct expansion and improves borderzone function after myocardial infarction: a study using magnetic resonance imaging, three-dimensional surface modeling, and myocardial tagging. *The Annals of Thoracic Surgery*. 2007; 84:2004–10. [PubMed: 18036925]
- [36]. Yankey GK, Li T, Kilic A, Cheng G, Satpute A, Savai K, et al. Regional remodeling strain and its association with myocardial apoptosis after myocardial infarction in an ovine model. *The Journal of Thoracic and Cardiovascular Surgery*. 2008; 135:991–8. 998.e1–2. [PubMed: 18455574]
- [37]. Morita M, Eckert CE, Matsuzaki K, Noma M, Ryan LP, Burdick JA, et al. Modification of infarct material properties limits adverse ventricular remodeling. *The Annals of Thoracic Surgery*. 2011; 92:617–24. [PubMed: 21801916]
- [38]. Gottlieb SO, Becker LC, Weiss JL, Shapiro EP, Chandra NC, Flaherty JT, et al. Nifedipine in acute myocardial infarction: an assessment of left ventricular function, infarct size, and infarct expansion. A double blind, randomised, placebo controlled trial. *Heart*. 1988; 59:411–8.
- [39]. Jugdutt BJ. Identification of patients prone to infarct expansion by the degree of regional shape distortion on an early two-dimensional echocardiogram after myocardial infarction. *Clinical Cardiology*. 1990; 13:28–40. [PubMed: 2297956]
- [40]. Jugdutt BI, Khan MI, Jugdutt SJ, Blinston GE. Effect of prolonged inotropic stimulation on ventricular remodeling during healing after myocardial infarction in the dog: Mechanistic insights. *Journal of the American College of Cardiology*. 1996; 27:1787–95. [PubMed: 8636569]
- [41]. Jackson BM, Gorman JH, Moainie SL, Guy TS, Narula N, Narula J, et al. Extension of borderzone myocardium in postinfarction dilated cardiomyopathy. *Journal of the American College of Cardiology*. 2002; 40:1160–7. [PubMed: 12354444]
- [42]. Mukherjee R. Myocardial Infarct Expansion and Matrix Metalloproteinase Inhibition. *Circulation*. 2003; 107:618–25. [PubMed: 12566376]

- [43]. Ahmet I, Krawczyk M, Heller P, Moon C, Lakatta EG, Talan MI. Beneficial effects of chronic pharmacological manipulation of beta-adrenoreceptor subtype signaling in rodent dilated ischemic cardiomyopathy. *Circulation*. 2004; 110:1083–90. [PubMed: 15313944]
- [44]. Ahmet I, Lakatta EG, Talan MI. Pharmacological stimulation of beta2-adrenergic receptors (beta2AR) enhances therapeutic effectiveness of beta1AR blockade in rodent dilated ischemic cardiomyopathy. *Heart Failure Reviews*. 2005; 10:289–96. [PubMed: 16583177]
- [45]. Ahmet I, Spangler E, Shukitt-Hale B, Joseph JA, Ingram DK, Talan M. Survival and cardioprotective benefits of long-term blueberry enriched diet in dilated cardiomyopathy following myocardial infarction in rats. *PloS One*. 2009; 4:e7975. Public Library of Science. [PubMed: 19936253]
- [46]. Ahmet I, Turner T, Lakatta EG, Talan MI. Fenoterol enantiomers do not possess beneficial therapeutic properties of their racemic mixture in the rat model of post myocardial infarction dilated cardiomyopathy. *Cardiovascular Drugs and Therapy / Sponsored by the International Society of Cardiovascular Pharmacotherapy*. 2012; 26:101–8. [PubMed: 22328006]
- [47]. Ahmet I, Tae H-J, Brines M, Cerami A, Lakatta EG, Talan MI. Chronic administration of small nonerythropoietic peptide sequence of erythropoietin effectively ameliorates the progression of postmyocardial infarction-dilated cardiomyopathy. *The Journal of Pharmacology and Experimental Therapeutics*. 2013; 345:446–56. [PubMed: 23584743]
- [48]. Ahmet I, Wan R, Mattson MP, Lakatta EG, Talan M. Cardioprotection by intermittent fasting in rats. *Circulation*. 2005; 112:3115–21. [PubMed: 16275865]
- [49]. Roberts CS, Maclean D, Maroko P, Kloner RA. Early and late remodeling of the left ventricle after acute myocardial infarction. *The American Journal of Cardiology*. 1984; 54:407–10. [PubMed: 6235736]
- [50]. Richard V, Murry CE, Reimer KA. Healing of myocardial infarcts in dogs. Effects of late reperfusion. *Circulation*. 1995; 92:1891–901. [PubMed: 7671374]
- [51]. Hillenbrand HB, Sandstede J, Störk S, Ramsayer B, Hahn D, Ertl G, et al. Remodeling of the infarct territory in the time course of infarct healing in humans. *Magma (New York, NY)*. 2011; 24:277–84.
- [52]. Theroux P, Ross J, Franklin D, Covell JW, Bloor CM, Sasayama S. Regional myocardial function and dimensions early and late after myocardial infarction in the unanesthetized dog. *Circulation Research*. 1977; 40:158–65. [PubMed: 844142]
- [53]. Jugdutt BI, Amy RWM. Healing after myocardial infarction in the dog: Changes in infarct hydroxyproline and topography. *Journal of the American College of Cardiology*. 1986; 7:91–102. American College of Cardiology Foundation. [PubMed: 3941223]
- [54]. Clarke SA, Goodman NC, Ailawadi G, Holmes JW. Effect of Scar Compaction on the Therapeutic Efficacy of Anisotropic Reinforcement Following Myocardial Infarction in the Dog. *Journal of Cardiovascular Translational Research*. 2015
- [55]. Popovi AD, Neškovi AN, Marinkovi J, Thomas JD. Acute and long-term effects of thrombolysis after anterior wall acute myocardial infarction with serial assessment of infarct expansion and late ventricular remodeling. *The American Journal of Cardiology*. 1996; 77:446–50. [PubMed: 8629582]
- [56]. Maclean D, Fishbein MC, Braunwald E, Maroko PR. Long-term preservation of ischemic myocardium after experimental coronary artery occlusion. *The Journal of Clinical Investigation*. 1978; 61:541–51. [PubMed: 641137]
- [57]. Miranda A, Costa-e-Sousa RH, Werneck-de-Castro JPS, Mattos EC, Olivares EL, Ribeiro VP, et al. Time course of echocardiographic and electrocardiographic parameters in myocardial infarct in rats. *Anais Da Academia Brasileira de Ciências*. 2007; 79:639–48. [PubMed: 18066433]
- [58]. Erlebacher JA, Weiss JL, Eaton LW, Kallman C, Weisfeldt ML, Bulkley BH. Late effects of acute infarct dilation on heart size: a two dimensional echocardiographic study. *The American Journal of Cardiology*. 1982; 49:1120–6. [PubMed: 6461240]
- [59]. Pfeffer J, Pfeffer M, Fletcher P, Braunwald E. Progressive ventricular remodeling in rat with myocardial infarction. *The American Journal of Physiology Heart and Circulatory Physiology*. 1991; 260:H1406–14.

- [60]. Boyle MP, Weisman HF. Limitation of infarct expansion and ventricular remodeling by late reperfusion. Study of time course and mechanism in a rat model. *Circulation*. 1993; 88:2872–83. [PubMed: 8252700]
- [61]. Golia G, Marino P, Rametta F, Nidasio GP, Prioli MA, Anselmi M, et al. Reperfusion reduces left ventricular dilatation by preventing infarct expansion in the acute and chronic phases of myocardial infarction. *American Heart Journal*. 1994; 127:499–509. [PubMed: 8122595]
- [62]. Jugdutt BI, Khan MI, Jugdutt SJ, Blinston GE. Effect of Enalapril on Ventricular Remodeling and Function During Healing After Anterior Myocardial Infarction in the Dog. *Circulation*. 1995; 91:802–12. [PubMed: 7828309]
- [63]. Guy TS, Moainie SL, Gorman JH, Jackson BM, Plappert T, Enomoto Y, et al. Prevention of ischemic mitral regurgitation does not influence the outcome of remodeling after posterolateral myocardial infarction. *Journal of the American College of Cardiology*. 2004; 43:377–83. [PubMed: 15013117]
- [64]. Weinheimer CJ, Lai L, Kelly DP, Kovacs A. Novel mouse model of left ventricular pressure overload and infarction causing predictable ventricular remodelling and progression to heart failure. *Clinical and Experimental Pharmacology & Physiology*. 2015; 42:33–40. [PubMed: 25311547]
- [65]. Gupta KB, Ratcliffe MB, Fallert MA, Edmunds LH, Bogen DK. Changes in passive mechanical stiffness of myocardial tissue with aneurysm formation. *Circulation*. 1994; 89:2315–26. [PubMed: 8181158]
- [66]. Holmes JW, Nuñez JA, Covell JW. Functional implications of myocardial scar structure. *The American Journal of Physiology*. 1997; 272:H2123–30. [PubMed: 9176277]
- [67]. McGarvey JR, Mojsejenko D, Dorsey SM, Nikou A, Burdick JA, Gorman JH, et al. Temporal Changes in Infarct Material Properties: An In Vivo Assessment Using Magnetic Resonance Imaging and Finite Element Simulations. *The Annals of Thoracic Surgery*. 2015; 100:582–9. [PubMed: 26095107]
- [68]. Kelley ST, Malekan R, Gorman JHI, Jackson BM, Gorman C, Suzuki Y, et al. Restraining infarct expansion preserves left ventricular geometry and function after acute anteroapical infarction. *Circulation*. 1999; 99:135–42. [PubMed: 9884390]
- [69]. Moainie SL, Guy TS, Gorman JHI, Plappert T, Jackson BM, St John-Sutton MG, et al. Infarct restraint attenuates remodeling and reduces chronic ischemic mitral regurgitation after posterolateral infarction. *The Annals of Thoracic Surgery*. 2002; 74:444–9. [PubMed: 12173827]
- [70]. Fujimoto KL, Tobita K, Merryman WD, Guan J, Momoi N, Stolz DB, et al. An elastic, biodegradable cardiac patch induces contractile smooth muscle and improves cardiac remodeling and function in subacute myocardial infarction. *Journal of the American College of Cardiology*. 2007; 49:2292–300. [PubMed: 17560295]
- [71]. Simpson D, Liu H, Fan T-HM, Nerem R, Dudley SC. A tissue engineering approach to progenitor cell delivery results in significant cell engraftment and improved myocardial remodeling. *Stem Cells*. 2007; 25:2350–7. [PubMed: 17525236]
- [72]. Chachques JC, Trainini JC, Lago N, Cortes-Morichetti M, Schussler O, Carpentier A. Myocardial assistance by grafting a new bioartificial upgraded myocardium (MAGNUM trial): clinical feasibility study. *The Annals of Thoracic Surgery*. 2008; 85:901–8. [PubMed: 18291168]
- [73]. Liao S-Y, Siu C-W, Liu Y, Zhang Y, Chan W-S, Wu EX, et al. Attenuation of left ventricular adverse remodeling with epicardial patching after myocardial infarction. *Journal of Cardiac Failure*. 2010; 16:590–8. Elsevier Inc. [PubMed: 20610235]
- [74]. Dai W, Wold LE, Dow JS, Kloner RA. Thickening of the infarcted wall by collagen injection improves left ventricular function in rats: a novel approach to preserve cardiac function after myocardial infarction. *Journal of the American College of Cardiology*. 2005; 46:714–9. [PubMed: 16098441]
- [75]. Landa N, Miller L, Feinberg MS, Holbova R, Shachar M, Freeman I, et al. Effect of injectable alginate implant on cardiac remodeling and function after recent and old infarcts in rat. *Circulation*. 2008; 117:1388–96. [PubMed: 18316487]

- [76]. Mukherjee R, Zavadzka JA, Saunders SM, McLean JE, Jeffords LB, Beck C, et al. Targeted myocardial microinjections of a biocomposite material reduces infarct expansion in pigs. *The Annals of Thoracic Surgery*. 2008; 86:1268–76. [PubMed: 18805174]
- [77]. Ryan LP, Matsuzaki K, Noma M, Jackson BM, Eperjesi TJ, Plappert TJ, et al. Dermal filler injection: a novel approach for limiting infarct expansion. *The Annals of Thoracic Surgery*. 2009; 87:148–55. The Society of Thoracic Surgeons. [PubMed: 19101288]
- [78]. Dobner S, Bezuidenhout D, Govender P, Zilla P, Davies N. A synthetic non-degradable polyethylene glycol hydrogel retards adverse post-infarct left ventricular remodeling. *Journal of Cardiac Failure*. 2009; 15:629–36. Elsevier Inc. [PubMed: 19700140]
- [79]. Leor J, Tuvia S, Guetta V, Manczur F, Castel D, Willenz U, et al. Intracoronary injection of in situ forming alginate hydrogel reverses left ventricular remodeling after myocardial infarction in Swine. *Journal of the American College of Cardiology*. 2009; 54:1014–23. [PubMed: 19729119]
- [80]. Ifkovits JL, Tous E, Minakawa M, Morita M, Robb JD, Koomalsingh KJ, et al. Injectable hydrogel properties influence infarct expansion and extent of postinfarction left ventricular remodeling in an ovine model. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:11507–12. [PubMed: 20534527]
- [81]. Rane, A. a; Chuang, JS.; Shah, A.; Hu, DP.; Dalton, ND.; Gu, Y., et al. Increased infarct wall thickness by a bio-inert material is insufficient to prevent negative left ventricular remodeling after myocardial infarction. *PloS One*. 2011; 6:e21571. [PubMed: 21731777]
- [82]. Berry MF, Engler AJ, Woo YJ, Pirolli TJ, Bish LT, Jayasankar V, et al. Regulation and Function of Stem Cells in the Cardiovascular System Mesenchymal stem cell injection after myocardial infarction improves myocardial compliance. 2006; 6085:2196–203.
- [83]. Wall ST, Walker JC, Healy KE, Ratcliffe MB, Guccione JM. Theoretical impact of the injection of material into the myocardium: a finite element model simulation. *Circulation*. 2006; 114:2627–35. [PubMed: 17130342]
- [84]. Barandon L, Couffignal T, Ezan J, Dufourcq P, Costet P, Alzieu P, et al. Reduction of infarct size and prevention of cardiac rupture in transgenic mice overexpressing FrzA. *Circulation*. 2003; 108:2282–9. [PubMed: 14581414]
- [85]. McKay RG, Aroesty JM, Heller GV, Royal HD, Warren SE, Grossman W. Assessment of the end-systolic pressure-volume relationship in human beings with the use of a time-varying elastance model. *Circulation*. 1986; 74:97–104. [PubMed: 3708783]
- [86]. Litwin SE, Katz SE, Morgan JP, Douglas PS. Serial echocardiographic assessment of left ventricular geometry and function after large myocardial infarction in the rat. *Circulation*. 1994; 89:345–54. [PubMed: 8281668]
- [87]. Jugdutt BI, Joljart MJ, Khan MI. Rate of collagen deposition during healing and ventricular remodeling after myocardial infarction in rat and dog models. *Circulation*. 1996; 94:94–101. [PubMed: 8964124]
- [88]. Saeed M, Watzinger N, Krombach GA, Lund GK, Wendland MF, Chujo M, et al. Left ventricular remodeling after infarction: sequential MR imaging with oral nicorandil therapy in rat model. *Radiology*. 2002; 224:830–7. Radiological Society of North America. [PubMed: 12202722]
- [89]. Ganame J, Messalli G, Masci PG, Dymarkowski S, Abbasi K, Van de Werf F, et al. Time course of infarct healing and left ventricular remodelling in patients with reperused ST segment elevation myocardial infarction using comprehensive magnetic resonance imaging. *European Radiology*. 2011; 21:693–701. [PubMed: 20865262]
- [90]. Sakai Y, Tsunoda K, Ishibashi I, Miyazaki Y, Takahashi O, Masuda Y. Time Course of Left Ventricular Remodeling After Myocardial Infarction. *Japanese Circulation Journal*. 2000; 64:421–9. [PubMed: 10875732]
- [91]. Gao X. Serial echocardiographic assessment of left ventricular dimensions and function after myocardial infarction in mice. *Cardiovascular Research*. 2000; 45:330–8. [PubMed: 10728353]

Fig. 1. Infarct dimension studies report both expansion and compaction

Studies that made quantitative measurements of in-plane (circumferential or longitudinal) dimensions at multiple healing time-points consistently showed expansion over the first 24 hours (A), but a mix of expansion (increased in-plane dimension), compaction (decreased), or insignificant change at later times (B). The balance of reported dimension changes differed when measurements were made in an unloaded (zero cavity pressure) or loaded state. [4,5,7,9,14,24–30,32–64,85]

Fig. 2. Healing infarcts thin, sometimes expand, and sometimes compact

Infarct dimensions from studies of rat, dog, pig, sheep, baboon, and patient infarcts were compared by calculating remodeled dimension ratios (thickness and in-plane) as the scar dimension at a given time relative to that dimension at the initial measurement at least 24h post-infarction [4,5,9,11,12,14,27,30–64,80,84,86–91]. Analysis shows that infarcts (1) consistently thin (A), (2) typically compact when measured in the unloaded state (B), and (3) sometimes expand and sometimes compact when measured in the pressurized LV (B).

Fig. 3. Infarct stiffening and thinning can lead to compaction or expansion

A finite-element model of an infarcted rat ventricle (A) and infarcted dog ventricle (D) were developed from gadolinium-enhanced MR images, and used to predict the changes in end-diastolic (loaded) infarct circumferential segment length resulting from changes in unloaded infarct stiffness or thickness (B, C, &E). End-diastolic circumferential dimension ratios increase (ratio>1, usually interpreted as in-plane infarct expansion) as the infarct thins, but decrease (ratio<1, in-plane compaction) as the infarct stiffens.

Table 1
Localized interventions have variable efficacy in preventing adverse remodeling and improving ejection fraction post-MI

We list here the reported effects of patches secured to the scar epicardial surface or materials injected into the scar wall on remodeled scar thickness, in-plane scar dimension, scar stiffness, LV end-diastolic volume or area (EDV), LV end-systolic volume or area (ESV), and functional measures including ejection fraction (EF), and fractional shortening (FS). Increases or decreases listed in the table signify statistically significant differences between the MI with therapy group and the MI with sham-therapy group. Material abbreviations: polypropylene (PP), polyester urethane urea (PEUU), mesenchymal stem cells (MSCs), bone marrow cells (BMCs), polytetrafluoroethylene (PTFE), polyethylene glycol (PEG), and methacrylated hyaluronic acid (MeHA). [68–81]

Reference	Model	Material	Thickness	In-plane	Stiffness	EDV	ESV	EF / FS
<i>Synthetic & Tissue-engineered Patches</i>								
Kelley 1999	sheep	PP	↑		↑ *	↓	↓	↑
Moainie 2002	sheep	PP		↓	↑ *	↔	↔	↔
Fujimoto 2007	rat	PEUU	↑		↓ #	↓		↑
Simpson 2007	rat	collagen	↔			↔	↔	↔
		coll.+MSCs	↑			↓	↓	↑
Chachques 2008	human	collagen+BMCs	↑			↓	↓	↔
Liao 2010	pig	PP + PTFE	↑		↑ *	↓	↓	↑
<i>Intramural Injections</i>								
Dai 2005	rat	collagen	↑	↑		↔	↔	↑
Landa 2008	rat (1wk)	alginate	↑			↓	↓	↔
	rat (6wks)		↑	↔		↔	↔	↔
Mukherjee 2008	pig	fibrin-alginate	↔	↓	↔ #	↔		↔
Ryan 2009	sheep	Radiesse®	↑			↓	↓	↑
Dobner 2009	rat	PEG	↔			↔	↔	↔
Leor 2009	pig	alginate	↑			↓	↓	↔
Ifkovits 2010	sheep	MeHA (low)	↑	↔	↔ †	↔	↔	↔
		MeHA (high)	↑	↓	↔ †	↔	↔	↔
Rane 2011	rat	PEG	↑			↔	↔	↔

* Assumed based on relative inextensibility of patch material

[#]Based on pressure-strain curves

[†]Tensile moduli

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