Published in final edited form as:

Can J Cardiol. 2012 ; 28(2): 230–238. doi:10.1016/j.cjca.2011.11.003.

Longitudinal Study of Cardiac Remodeling in Rabbits Following Infarction

Yves T. Wang, M.S.^{1,2}, Zoran B. Popovi , M.D., Ph.D.³, Igor R. Efimov, Ph.D.⁴, and Yuanna Cheng, M.D., Ph.D.^{1,2,3}

¹Department of Molecular Cardiology, Cleveland Clinic, Cleveland, OH

²Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH

³Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH

⁴Department of Biomedical Engineering, Washington University, St. Louis, MO

Abstract

Background—Cardiac remodeling following myocardial infarction (MI) is a complex, dynamic process. There have been few longitudinal studies of these changes.

Methods—Two-dimensional transthoracic echocardiography was performed on 20 rabbits: before and 1, 2, 4, 8, and 12 weeks after MI (n=14) and twice for controls (n=6). Chronic left ventricular (LV) infarct size was histologically characterized and correlated with mechanical function. A linear mixed model was used to analyze longitudinal and infarct size related changes in LV end-systolic volume (ESV), end-diastolic volume (EDV), ejection fraction (EF), sphericity, circumferential strain, and wall motion score index (WMSI).

Results—Mean LV infarct size was 28.9±9.3%. After MI, rapid remodeling occurred in LVESV, LVEF, and sphericity for 2 weeks and LVEDV for 4 weeks, with slower changes afterwards. LV infarct size correlated with LVESV (r=0.76), LVEDV (r=0.71), and LVEF (r=0.69). Larger infarcts resulted in greater LVESV dilation (p=0.04) and faster LVEDV (p<0.01), LVEF (p<0.01) and sphericity (p<0.01) remodeling. Apical global circumferential strain and WMSI increased for 1 week then stabilized, regardless of infarct size, and apical global circumferential strain was correlated with apical infarction (r=0.58). Additionally, regional circumferential strain decreased in segments with severe (>80%) infarction more quickly (p<0.01) and by a greater degree (p=0.04) compared to segments with minor (<20%) infarction.

Address reprint requests and correspondence: Yuanna Cheng, M.D., Ph.D., Department of Molecular Cardiology, NE61, Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, Phone: (216) 445-7823, Fax: (216) 445-4166, chengy@ccf.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

DISCLOSURES

No conflicts of interest.

Conclusions—The most dynamic remodeling of cardiac function in this model occurred during the first 4 weeks, stabilizing thereafter, with changes maintained up to 12 weeks. Infarct size affected both the early rate and long-term extent of mechanical remodeling.

INTRODUCTION

Cardiac remodeling following myocardial infarction (MI) is a complex process that involves dynamic changes in the mechanical, structural, and electrical properties of the heart.^{1,2} The rabbit model is frequently used for investigating MI.³ Compared to smaller animals, rabbit hearts bear a greater resemblance to that of humans, including increased similarity in ventricular action potential morphology,⁴ calcium handling,⁵ and myosin heavy chain composition.⁶ Additionally, rabbits and humans both have limited collateral cardiac circulation.⁷ This model allows regional ischemia to be produced by occluding coronary arteries and facilitates assessment of the histopathologic development of infarction.⁸

Post-MI changes in cardiac function can be quickly, easily, inexpensively, and noninvasively characterized repeatedly using echocardiography. Echocardiographic studies have shown that MI frequently leads to left ventricular (LV) dilation, resulting in increased end-systolic volume (ESV) and end-diastolic volume (EDV), decreased ejection fraction (EF), and increased sphericity that can lead to heart failure.^{9–11} Understanding the time courses of these changes is important for designing experiments to test interventions. Clinical and animal studies have shown that remodeling begins within hours following an MI and continues for months.^{12–15} However, this remodeling has not been longitudinally documented in rabbits. Additionally, many studies have used cross-sectional rather than longitudinal analyses, ignoring the correlated nature of repeated measurements. Moreover, while infarct size and mechanical remodeling are correlated,^{16–19} the effects of infarct size on the time courses of remodeling are not well characterized.

Speckle-tracking echocardiography can assess global and regional wall strains, a quantitative measure of wall motion. It detects interference patterns (speckles) created by the interaction between the frequency and angle of the ultrasound beam and the imaged tissue²⁰ and that provide markers for determining tissue movement, allowing strains to be measured anywhere in B-mode images. Wall motion score index (WMSI) is another commonly used, semiquantitative measure of global wall motion.²¹ Post-MI, circumferential strain decreases²² and WMSI increases,²³ but the time course of these changes has not been well studied nor has the impact of infarct size on the time course of this remodeling.

This study sought to longitudinally follow cardiac remodeling in a rabbit MI model using repeated echocardiographs up to 12 weeks post-MI to characterize the time course and extent of changes in cardiac function and wall motion and to examine the impact of infarct size on these changes.

METHODS

All animal protocols were approved by the Institutional Animal Care and Use Committee of the Cleveland Clinic. All animals used in this study received humane care in compliance

with the National Institutes of Health's *Guide for the Care and Use of Laboratory Animals* (NIH publication 85–23, revised 1996).

Animal MI Model

Data from 20 male New Zealand White rabbits were used in this study. Fourteen animals had an MI created by ligation of the lateral or posterolateral division of the left coronary artery (LCA),^{24,25} based on LCA distribution.²⁶ The ligation was made approximately midway between the LV apex and base. Two animals intended for this study died before completion and were excluded (2/16, 12.5%). See Online Methods for details. Six control animals did not undergo any surgery.

Echocardiography

Non-invasive, two-dimensional transthoracic echocardiography was performed on MI rabbits pre-surgery (0 week) and 1, 2, 4, 8, and 12 weeks post-surgery. Controls were imaged twice, 9 weeks apart. Animals lightly sedated by 35 mg/kg ketamine administered intramuscularly were imaged using a GE Vivid 7 with a 10S transducer (GE Medical, Milwaukee, WI). Good quality parasternal long- and short-axis images were obtained in all cases.

Measurements of LVESV, LVEDV, LVEF, sphericity, circumferential strain, and wall motion score index (WMSI) were made using GE EchoPac software. Sphericity was calculated as the ratio of diastolic short-axis to long-axis lengths.²⁷ Strains were measured using speckle-tracking for the entire LV plane (global) and each of 6 segments (regional; Figure 1 A) near the papillary muscles and near the apex.²² WMSI was calculated using 16-segments, with higher scores indicating greater wall motion abnormalities.²¹ See Online Methods for details.

Histology

Histology was performed on Masson's Trichrome stained transverse sections of O.C.T. (Sakura Finetek, Torrance, CA) embedded ventricles collected after the final echocardiographic study (> 8 weeks post-MI). The LV was digitally isolated (Figure 1 A), and chronic LV infarction was evaluated using a length-circumference method.²⁸ Total and infarct tissue traces for each section were measured. For total chronic LV infarct size, the infarct tissue traces were piecewise linearly integrated across all sections and normalized by the integrated total tissue traces. Chronic infarction for planes corresponding to short-axis echocardiographic images and segmental chronic infarction for the 6 segments matching those of apical regional circumferential strain (Figure 1 A) were also determined. See Online Methods for details.

Statistical Analysis

To assess longitudinal changes, a linear mixed effects model with unstructured covariance for random effects was applied using SPSS (SPSS Inc., Chicago, IL).^{29,30} A linear spline model with one break point was used to fit the data. See Online Methods for details.

Correlations between infarct size and other parameters were tested using simple linear regression and their strengths were evaluated by Pearson's r .

Model data are presented as mean $\pm$ SE to reflect the uncertainty of calculated model parameters. Measured data are presented as mean $\pm$ SD to reflect the spread of measurements. The threshold for statistical significance was $p < 0.05$.

RESULTS

Histological Characterization of Chronic Infarction

Histologic analysis showed that transmural infarcts covered most of the apical region (Figure 1 A–B) in all hearts. Further from the apex, infarcts were predominantly on the LV free wall, in agreement with our previous reports regarding this model.^{24,25} Mean LV infarct size was $28.9 \pm 9.3\%$ ($n = 14$). Hearts were dichotomized by infarct size at the median value of 28.8% (Figure 1 C–D, $n = 7$ each).

Histologic sections matched to echocardiographic short-axis planes confirmed that the papillary muscle plane was unaffected (0%) while the apical plane was severely infarcted ($66.6 \pm 14.5\%$). All hearts had at least one apical segment with severe infarction ($> 80\%$ fibrosis; 3.6 ± 1.1 segments) and at least one with minor infarction ($< 20\%$; 1.4 ± 0.6 segments). Generally, the posterior (13 of 14 hearts), lateral (12), and inferior (10) segments had severe infarction while the anteroseptal segment had minor infarction (11).

Cardiac Function (LVESV, LVEDV, LVEF, and Sphericity)

Pre-surgery (Figure 2 A–C, 0 week), MI and control groups had similar LVESV, LVEDV, LVEF and sphericity ($p = 0.15, 0.58, 0.18$, and 0.17 respectively). After MI, the optimal break point for the linear spline model was 2 weeks for LVESV, LVEF, and sphericity and 4 weeks for LVEDV (Figure 2 A–C, circles and solid lines). Early remodeling was rapid (LVESV: 0.39 ± 0.03 mL/week, LVEDV: 0.24 ± 0.03 mL/week, LVEF: -6.63 ± 0.66 mL/week, sphericity: 0.078 ± 0.004 /week, $p < 0.01$ for all). After the break points, continued trends of late remodeling (LVESV: 0.07 ± 0.04 mL/week, LVEDV: 0.02 ± 0.03 mL/week, LVEF: -0.43 ± 0.50 mL/week; sphericity: -0.002 ± 0.002 /week) were not statistically significant ($p = 0.05, 0.53, 0.39$, and 0.33 , respectively). Controls had no break point or significant change for LVESV, LVEDV, LVEF, or sphericity ($p = 0.64, 0.90, 0.33$, and 0.96 , respectively; Figure 2 A–C, triangles and dotted lines).

Global Wall Motion (Circumferential Strain and WMSI)

Papillary muscle global circumferential strain was similar between groups ($p = 0.42$), and neither changed significantly (MI: $p = 0.76$, control: $p = 0.90$; Figure 2 D). At the apical plane, MI hearts had a break point at 1 week with rapid early remodeling ($4.74 \pm 0.47\%$ /week, $p < 0.01$; Figure 2 E, circles and solid line). Late remodeling continued at a reduced rate ($0.46 \pm 0.49\%$ /week), but was not significant ($p = 0.25$). Control hearts showed no change in apical circumferential strain ($p = 0.75$; Figure 2 E, triangles and dotted line).

MI hearts had a WMSI of 1 pre-surgery (0 weeks) and a break point at 1 week with rapid early remodeling (0.38 ± 0.01 /week, $p < 0.01$; Figure 2 F, circles and solid line). Late

remodeling was not significant ($0.01 \pm 0.02/\text{week}$, $p = 0.44$). Post-MI, only apical segments had abnormal wall motion and were generally akinetic (Table 1). Control hearts had normal WMSI (Figure 2 F, triangles and dotted line).

Correlation with Infarct Size

LV infarct size was correlated with the final measurements of LVESV ($p < 0.01$, $r = 0.76$), LVEDV ($p < 0.01$, $r = 0.71$), and LVEF ($p < 0.01$, $r = 0.69$; Figure 3 A–C). LV infarct size was not significantly correlated with sphericity, global circumferential strain at either plane, or WMSI ($p = 0.39, 0.19, 0.12$, and 0.62 respectively; plots not shown). Final measurements of apical global circumferential strain were correlated with the infarction of that plane ($p = 0.03$, $r = 0.58$; Figure 3 D).

Effect of Infarct Size

MI hearts dichotomized at the median LV infarct size (28.8%) had mean infarct sizes of $36.8 \pm 4.5\%$ (larger MI, LMI) and $20.9 \pm 4.3\%$ (smaller MI, SMI; Figure 1 C–D, $p < 0.01$, $n = 7$ each). For both groups, the break point for LVESV remained at 2 weeks (Figure 4 A). However, early LVESV dilation in LMI hearts was faster ($0.47 \pm 0.05 \text{ mL/week}$ vs. $0.33 \pm 0.04 \text{ mL/week}$, $p = 0.04$), while late remodeling rates were similar ($p = 0.98$), resulting in a continued significant difference 12 weeks post-MI.

For LVEDV, the break point for LMI hearts occurred at 2 weeks, but remained at 4 weeks for SMI hearts (Figure 4 A), with significantly different early remodeling rates ($0.44 \pm 0.03 \text{ mL/week}$ vs. $0.21 \pm 0.03 \text{ mL/week}$, $p < 0.01$). Late remodeling rates ($p = 0.60$) and the extent of remodeling after 4 weeks ($p = 0.73$) were similar.

For LVEF, the break point was at 1 week for LMI hearts and 2 weeks for SMI hearts (Figure 4 B). Early remodeling rates were significantly different ($-12.83 \pm 1.37\%/\text{weeks}$ vs. $-6.11 \pm 1.02\%/\text{week}$, $p < 0.01$). After 2 weeks post-MI, both the extent ($p = 0.74$) and rate ($p = 0.80$) were comparable.

For sphericity, LMI hearts had a break point at 1 week while the break point for SMI hearts remained at 2 weeks (Figure 4 C). The early remodeling rate was significantly greater in LMI hearts ($0.128 \pm 0.008/\text{week}$ vs. $0.074 \pm 0.006/\text{week}$, $p < 0.01$). After 2 weeks, the extent ($p = 0.21$) and rate ($p = 0.67$) were similar.

For global circumferential strain, the time course and extent of remodeling at either plane was similar between groups (Figure 4 D–E). Both had similar papillary muscle global circumferential strains ($p = 0.21$) without significant remodeling (LMI: $p = 0.18$, SMI: $p = 0.82$). At the apical plane, both groups had a break point at 1 week. While early remodeling of the LMI hearts was faster ($5.62 \pm 0.82\%/\text{week}$ vs. $4.61 \pm 0.83\%/\text{week}$), the difference was not significant ($p = 0.44$). The rate of late remodeling was similar between groups ($p = 0.99$), so the extent of remodeling remained similar.

For WSMI, break points remained at 1 week, with no significant differences in the rate of early ($p = 0.90$) or late ($p = 0.78$) remodeling between groups (Figure 4 F).

Regional Circumferential Strain

In segments with severe infarction ($> 80\%$), circumferential strain decreased rapidly ($7.55 \pm 0.72\%/week$) until a break point at 1 week (Figure 5 A). In segments with minor infarction ($< 20\%$), circumferential strain decreased more slowly ($0.75 \pm 0.47\%/week$) with a break point at 4 weeks (Figure 5 B). Early rates of change were significantly different ($p < 0.01$), and the values after the break points remained significantly different ($p = 0.04$), while the late remodeling rates were similar ($p = 0.92$).

DISCUSSION

This study shows that early LV remodeling after infarction results in rapid changes to mechanical function over 1–4 weeks, followed by slower changes up to 12 weeks post-MI. Larger LV infarcts promoted shorter, more rapid early remodeling for LVEDV, LVEF, and sphericity and a greater extent of remodeling for LVESV. Wall motion abnormalities also increased early, but were unaffected by LV infarct size. All apical segments had a long-term reduction of strain, but more infarcted segments remodeled to a greater extent and more quickly.

Cardiac Function

This rabbit study shows that remodeling occurs rapidly during an initial period followed by slower changes, similar to observations in mice,¹³ rats,^{12,19} and humans.^{14,31} Changes in LVESV, LVEDV, LVEF, and sphericity were initially rapid (1–4 weeks after MI); later remodeling (up to 12 weeks) was not significant.

In agreement with previous studies,^{16,18} chronic LV infarct size was correlated with LV volumes and LVEF. This study further demonstrates a relationship between infarct size and the time course of remodeling, with larger infarcts resulting in shorter periods of LVEDV, LVEF, and sphericity remodeling.

Global Wall Motion

This study presents the novel observation that changes in apical wall motion follow the same temporal pattern as cardiac function, with rapid initial changes happening over the first week followed by slower late remodeling. This may reflect necrosis of infarct region myocytes,³² resulting in impaired contractile ability and thus a reduction of strains within hours. Correlation between the apical global circumferential strain and the degree of apical infarction as well as the akinesis of the majority of apical segments further support this. Away from the infarct, no significant changes in wall motion were observed, indicating no significant compensatory effect. Contrary to previous reports,²³ no significant correlation was found between WMSI and infarct size, probably due to the narrow range of WMSI in this study (1.19–1.69).

Regional Circumferential Strain

In this study, infarcts predominantly affected the LV free wall, but some extended more towards the inferior while others towards the anterior, due to the varying LCA distribution.³³ So, segmental strains were grouped based on the degree of infarction rather

than location. This study makes the novel observation that regional circumferential strains were reduced in all apical LV segments of the studied hearts regardless of the degree of segmental infarction. However, segments with more severe infarction remodeled more quickly and to a greater extent.

Statistical Analysis

Most animal studies examining the time course of changes post-MI have used repeated measures analysis of variance (RM-ANOVA). While RM-ANOVA was historically used for longitudinal data, it is not optimal due to the correlated nature of longitudinal data. RM-ANOVA assumes compound symmetry, where the variances and covariances are constant; this assumption is generally not valid for longitudinal data. Here, we used a linear mixed model, a more recent and powerful statistical method designed for this type of experimental data. This longitudinal study design and analysis provide greater power to the statistical inferences than a crosssectional study design and analysis and is minimally affected by missing data.

Several models were considered before a linear spline model with one break point was chosen as the best fit based on information criteria and residual analysis. The results of this study are in agreement with previous studies that used cross-sectional analyses, showing that remodeling of mechanical function occurs in 2 distinct phases. This longitudinal study further provides the new findings that LV infarct size affects the time course of remodeling for cardiac function but not wall motion, and that regional circumferential strain remodeling is dependent on segmental infarction.

Study Limitations

The rabbit MI model used in this study is somewhat limited in the maximum infarct size, as efforts to create very large infarcts result in unacceptably high mortality rates.²⁶ In other models and in humans, infarcts can be over 50% of the LV.^{16,18} Nevertheless, a wide range of LV infarct sizes was produced (16–43%), and significant differences were observed. However, very larger infarcts would likely result in faster and greater remodeling post-MI, increasing the differences in the speed and degree of remodeling between groups. Inclusion of smaller infarcts (< 15%), which would likely cause minimal remodeling, would also be expected to increase the observed differences between groups. Additionally, while the sample sizes of the dichotomized groups were sufficient, larger groups may have improved the confidence of the results and increased the statistical significance of the differences.

Follow-up echocardiography was not performed in the first days following MI, as the additional procedural and anesthesia-related stress shortly after surgery might have triggered lethal arrhythmias. Earlier exams may have revealed differences in the duration of early remodeling between groups for LVESV or apical global circumferential strain. Additionally, early remodeling (< 72 h post-MI)^{13–15,34} was completed before the first follow-up. As a result, this study was unable to document either the dilation of the infarct region until after it was essentially complete or the peak of wall motion abnormalities in infarct segments.¹⁵ Extended follow-ups may also have yielded more significant differences in late remodeling.

Anesthetic drugs have known cardiac effects,^{35,36} so a minimal dose of ketamine (35 mg/kg) was administered without xylazine during echocardiographic studies. Animals were treated similarly for all studies, and heart rates pre-surgery (213 ± 21 beats per minute) are comparable to values previously reported for awake, unrestrained rabbits.³⁷

This study examined common indices of mechanical function that are affected by MI. However, other parameters may follow a different time course. Additionally, the mechanical, structural, and electrical remodeling post-MI involve interrelated processes. Changes in structural and electrical properties of the heart contribute to mechanical changes. This study used echocardiography to assess only the overall mechanical remodeling.

Conclusions

This is the first study to present a detailed longitudinal study of mechanical remodeling in rabbits, a frequently used MI model. The most rapid and dynamic remodeling of cardiac function and wall motion occurred during the first 4 weeks following MI. Afterwards, cardiac function and wall motion stabilized, and changes were maintained up to 12 weeks. Also, this study demonstrates that infarct size is not only correlated with the extent of long-term cardiac function remodeling, but also affects the rate and duration of the early dynamic changes. These findings may aid in the design of future experiments to test interventions following MI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Jackie Kattar and William Kowalewski of the Atrial Fibrillation Innovation Center for their surgical assistance and Dr. David Van Wagoner for reviewing this article.

FUNDING SOURCES: This study was supported by the American Heart Association (Wang: 0815500D; Cheng: 0655154B) and the National Institutes of Health (Efimov: R01 HL074283).

References

1. St John SM, Lee D, Rouleau JL, et al. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction. *Circulation*. 2003 May 27; 107(20):2577–82. [PubMed: 12732606]
2. Armoundas AA, Wu R, Juang G, Marban E, Tomaselli GF. Electrical and structural remodeling of the failing ventricle. *Pharmacol Ther*. 2001 Nov; 92(2–3):213–30. [PubMed: 11916538]
3. Verdouw PD, van den Doel MA, de ZS, Duncker DJ. Animal models in the study of myocardial ischaemia and ischaemic syndromes. *Cardiovasc Res*. 1998 Jul; 39(1):121–35. [PubMed: 9764194]
4. Bassani RA, Altamirano J, Puglisi JL, Bers DM. Action potential duration determines sarcoplasmic reticulum Ca²⁺ reloading in mammalian ventricular myocytes. *J Physiol*. 2004 Sep 1; 559(Pt 2): 593–609. [PubMed: 15243136]
5. Pogwizd SM, Bers DM. Rabbit models of heart disease. *Drug Discovery Today: Disease Models*. 2008; 5(3):185–93.
6. Marian AJ. On Mice, Rabbits, and Human Heart Failure. *Circulation*. 2005 May 10; 111(18):2276–9. [PubMed: 15883223]
7. Ytrehus K. The ischemic heart—experimental models. *Pharmacol Res*. 2000 Sep; 42(3):193–203. [PubMed: 10945923]

8. Morales C, Gonzalez GE, Rodriguez M, Bertolasi CA, Gelpi RJ. Histopathologic time course of myocardial infarct in rabbit hearts. *Cardiovasc Pathol*. 2002 Nov; 11(6):339–45. [PubMed: 12459435]
9. Vitarelli A, Tiukinhoy S, Di LS, Zampino M, Gheorghiade M. The role of echocardiography in the diagnosis and management of heart failure. *Heart Fail Rev*. 2003 Apr; 8(2):181–9. [PubMed: 12766498]
10. Nicolosi GL. Echocardiography to understand remodeling and to assess prognosis after acute myocardial infarction. *Int J Cardiol*. 1998 May 29; 65(Suppl 1):S75–S78. [PubMed: 9706832]
11. Sabbah HN, Kono T, Stein PD, Mancini GB, Goldstein S. Left ventricular shape changes during the course of evolving heart failure. *Am J Physiol*. 1992 Jul; 263(1 Pt 2):H266–H270. [PubMed: 1636764]
12. 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 Jan; 89(1):345–54. [PubMed: 8281668]
13. Thibault H, Gomez L, Donal E, et al. Regional myocardial function after myocardial infarction in mice: a follow-up study by strain rate imaging. *J Am Soc Echocardiogr*. 2009 Feb; 22(2):198–205. [PubMed: 19121566]
14. Otasevic P, Neskovic AN, Popovic Z, et al. Short early filling deceleration time on day 1 after acute myocardial infarction is associated with short and long term left ventricular remodelling. *Heart*. 2001 May; 85(5):527–32. [PubMed: 11303004]
15. 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. *J Am Coll Cardiol*. 1988 Jan; 11(1):177–85. [PubMed: 3335694]
16. Kanno S, Lerner DL, Schuessler RB, et al. Echocardiographic evaluation of ventricular remodeling in a mouse model of myocardial infarction. *J Am Soc Echocardiogr*. 2002 Jun; 15(6):601–9. [PubMed: 12050601]
17. Pfeffer MA, Pfeffer JM, Fishbein MC, et al. Myocardial infarct size and ventricular function in rats. *Circ Res*. 1979 Apr; 44(4):503–12. [PubMed: 428047]
18. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation*. 1990 Apr; 81(4):1161–72. [PubMed: 2138525]
19. Pfeffer JM, Pfeffer MA, Fletcher PJ, Braunwald E. Progressive ventricular remodeling in rat with myocardial infarction. *Am J Physiol*. 1991 May; 260(5 Pt 2):H1406–H1414. [PubMed: 2035662]
20. Teske AJ, De Boeck BW, Melman PG, Sieswerda GT, Doevendans PA, Cramer MJ. Echocardiographic quantification of myocardial function using tissue deformation imaging, a guide to image acquisition and analysis using tissue Doppler and speckle tracking. *Cardiovasc Ultrasound*. 2007; 5:27. [PubMed: 17760964]
21. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005 Dec; 18(12):1440–63. [PubMed: 16376782]
22. Popovic ZB, Benejam C, Bian J, et al. Speckle-tracking echocardiography correctly identifies segmental left ventricular dysfunction induced by scarring in a rat model of myocardial infarction. *Am J Physiol Heart Circ Physiol*. 2007 Jun; 292(6):H2809–H2816. [PubMed: 17277023]
23. Zhang Y, Takagawa J, Sievers RE, et al. Validation of the wall motion score and myocardial performance indexes as novel techniques to assess cardiac function in mice after myocardial infarction. *Am J Physiol Heart Circ Physiol*. 2007 Feb; 292(2):H1187–H1192. [PubMed: 17028161]
24. Li L, Nikolski V, Wallick DW, Efimov IR, Cheng Y. Mechanisms of enhanced shock-induced arrhythmogenesis in the rabbit heart with healed myocardial infarction. *Am J Physiol Heart Circ Physiol*. 2005 Sep; 289(3):H1054–H1068. [PubMed: 15879480]
25. Kim SC, Vasanji A, Efimov IR, Cheng Y. Spatial distribution and extent of electroporation by strong internal shock in intact structurally normal and chronically infarcted rabbit hearts. *J Cardiovasc Electrophysiol*. 2008 Oct; 19(10):1080–9. [PubMed: 18479336]

26. Lee BH, Kim WH, Choi MJ, Rho JR, Kim WG. Chronic heart failure model in rabbits based on the concept of the bifurcation/trifurcation coronary artery branching pattern. *Artif Organs*. 2002 Apr; 26(4):360–5. [PubMed: 11952507]
27. Wong SP, French JK, Lydon AM, et al. Relation of left ventricular sphericity to 10-year survival after acute myocardial infarction. *Am J Cardiol*. 2004 Nov 15; 94(10):1270–5. [PubMed: 15541243]
28. Takagawa J, Zhang Y, Wong ML, et al. Myocardial infarct size measurement in the mouse chronic infarction model: comparison of area- and length-based approaches. *J Appl Physiol*. 2007 Jun; 102(6):2104–11. [PubMed: 17347379]
29. Verhaert D, Grimm RA, Puntawangkoon C, et al. Long-term reverse remodeling with cardiac resynchronization therapy: results of extended echocardiographic follow-up. *J Am Coll Cardiol*. 2010 Apr 27; 55(17):1788–95. [PubMed: 20413027]
30. Fitzmaurice, G.; Laird, N.; Ware, J. *Applied Longitudinal Analysis*. Hoboken, NJ: John Wiley & Sons, Inc; 2004.
31. Ganame J, Messalli G, Masci PG, et al. Time course of infarct healing and left ventricular remodelling in patients with reperfused ST segment elevation myocardial infarction using comprehensive magnetic resonance imaging. *Eur Radiol*. 2011 Apr; 21(4):693–701. [PubMed: 20865262]
32. Miura T, Downey JM, Ooiwa H, et al. Progression of myocardial infarction in a collateral flow deficient species. *Jpn Heart J*. 1989 Sep; 30(5):695–708. [PubMed: 2614932]
33. Podesser B, Wollenek G, Seitelberger R, et al. Epicardial branches of the coronary arteries and their distribution in the rabbit heart: the rabbit heart as a model of regional ischemia. *Anat Rec*. 1997 Apr; 247(4):521–7. [PubMed: 9096792]
34. St John Sutton M, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation*. 2000 Jun 27; 101(25):2981–8. [PubMed: 10869273]
35. Sanford TD, Colby ED. Effect of xylazine and ketamine on blood pressure, heart rate and respiratory rate in rabbits. *Lab Anim Sci*. 1980 Jun; 30(3):519–23. [PubMed: 7431851]
36. Stypmann J, Engelen MA, Breithardt AK, et al. Doppler echocardiography and tissue Doppler imaging in the healthy rabbit: differences of cardiac function during awake and anaesthetised examination. *Int J Cardiol*. 2007 Feb 7; 115(2):164–70. [PubMed: 16806537]
37. Marano G, Grigioni M, Tiburzi F, Vergari A, Zanghi F. Effects of isoflurane on cardiovascular system and sympathovagal balance in New Zealand white rabbits. *J Cardiovasc Pharmacol*. 1996 Oct; 28(4):513–8. [PubMed: 8891875]

Figure 1. Infarct size by histology

(A) Representative histologic image of the LV apical plane stained with Masson's Trichrome. Myocytes are red and fibrotic tissues are blue. Segments for regional strain measurements are marked. Cross-sectional total tissue (green) and infarct tissue (red) lengths are shown averaged across (B) all hearts (n = 14), (C) hearts with LV infarcts > 29% (n = 7), and (D) hearts with LV infarcts < 29% (n = 7). Longitudinal positions were normalized by total ventricular length and intermediate values interpolated. Traces are only shown where data was available for all hearts. Solid lines represent the means and dashed lines the standard deviations. Anterior (A), anterioseptal (AS), inferior (I), lateral (L), posterior (P), septal (S).

Figure 2. Time courses of cardiac remodeling

(A) LV volumes, (B) LVEF, (C) sphericity, (D) PM global circumferential strain, (E) AP global circumferential strain, and (F) WMSI. MI hearts (n = 14) are represented by circles and control hearts (n = 6) by triangles with error bars representing the standard deviation. Linear spline fits obtained by linear mixed model analysis are plotted (MI: solid line, control: dashed line). P-values indicate the significance of differences between fitted models post-MI. Apical (AP), papillary muscle (PM).

Figure 3. Correlation of echocardiography measurements and LV infarct size

Simple linear regression was used to assess correlation between LV infarct size and (A) LVESV, (B) LVEDV, and (C) LVEF. (D) The correlation between the infarction of the apical plane and AP global circumferential strain was similarly examined. Apical (AP).

Figure 4. Effect of LV infarct size on the time courses of cardiac remodeling

LV infarct size was added to the model as a dichotomized variable to create 2 equally sized groups divided at the median value ($> 29\%$ infarct: circles, solid lines, $< 29\%$ infarct: triangles, dotted lines). Comparisons between groups were made for (A) LV volumes, (B) LVEF, (C) sphericity, (D) PM global circumferential strain, (E) AP global circumferential strain, and (F) WMSI. P-values indicate the significance of differences between fitted models post-MI, divided into early (before both breakpoints) and late (after both breakpoints). Apical (AP), papillary muscle (PM).

Figure 5. Time courses of apical regional strain

(A) Average regional circumferential strain across segments with severe infarction (> 80%) and (B) segments with minor infarction (< 20%). P-values indicate the significance of differences between fitted models after 0 weeks and before both breakpoints (early) and after both breakpoints (late).

Table 1

Wall motion score index.

Time Point (weeks)	Mean number of apical segments by classification of motion				
	Normal (1)	Hypokinetic (2)	Akinetic (3)	Dyskinetic (4)	Aneurysmal (5)
0	4	0	0	0	0
1	0.71 ± 0.61 [*]	0.93 ± 0.62 [*]	2.29 ± 0.83 [*]	0.07 ± 0.27	0
2	0.43 ± 0.65 [*]	0.93 ± 0.83 [*]	2.57 ± 0.76 [*]	0.07 ± 0.27	0
4	0.29 ± 0.47 [*]	0.64 ± 0.63 [*]	2.79 ± 0.89 [*]	0.29 ± 0.83	0
8	0.17 ± 0.39 [*]	0.50 ± 0.52 [*]	3.17 ± 0.72 [*]	0.17 ± 0.39	0
12	0 [*]	0.75 ± 0.71 [*]	2.88 ± 0.83 [*]	0.38 ± 0.74	0

Group data for the 14 MI hearts showing the mean number of apical segments by classification of motion at each time point. All non-apical segments had normal wall motion at all time points.

^{*} p < 0.01 vs. week 0 (pre-surgery).