Ventricular Preexcitation Modulates Strain and Attenuates Cardiac Remodeling in a Swine Model of Myocardial Infarction

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Background—Myocardial infarction modifies the distribution of stress within the heart, increasing wall stress in ischemic and surrounding tissue, which often leads to adverse left ventricular remodeling. Electrical preexcitation pacing with appropriate timing of high-stress regions can reduce local strain and may attenuate global remodeling.

Methods and Results—Myocardial infarction was induced in 24 swine to study the short-term (n=12) and long-term (n=12) effects of therapy. Sonomicrometry and hemodynamic measurements were used to show the mechanistic effects of preexcitation and to determine the optimal stimulation site and atrioventricular delay. Lagrangian strain was used to assess regional loading characteristics. Long-term study animals were randomized to 8 weeks of preexcitation (therapy) or no pacing (control). Echocardiograms were performed 2 days after myocardial infarction and repeated at 60 days, when tissue weights and apoptosis were assessed. Preexcitation reduced regional strain in the short term, with the best results achieved when the border region was paced at an atrioventricular delay of 50% of the intrinsic PR interval. In the long term, the changes in left ventricular internal diameter and left atrial size were decreased in therapy animals versus control animals (0.9±0.3 versus 1.5±0.5 cm, P=0.03, and 1.06±0.78 versus 2.32±0.88 cm, P<0.04, respectively). Heart weight was significantly lower in the therapy animals than in the control animals (319.8±20.8 versus 359.6±29.3 g, P=0.02). Although not significant, cardiomyocyte apoptosis trended lower in the therapy group.

Conclusions—Preexcitation of the left ventricle after myocardial infarction reduced strain and stroke work in the infarct and border regions in the short term and attenuated adverse ventricular remodeling in the long term. (Circulation. 2007;116:1162-1169.)

Key Words: myocardial infarction ■ remodeling ■ heart failure ■ myocardial contraction ■ electrical stimulation

Despite recent advances in medical management after acute myocardial infarction (MI), a significant percentage of the 7.2 million patients with MI progress to heart failure and arrhythmic or pump failure death. It has been shown that MI modifies the distribution of wall stress within the heart, increasing stress in the ischemic and immediately surrounding regions. Increases in wall stress are associated with adverse left ventricular (LV) structural remodeling and LV dysfunction, which lead to neurohormonal and cytokine activation that results in poor clinical outcomes. Unloading the LV with vasodilators and cardiac support devices reduces wall stress, which may be one mechanism by which these devices attenuate adverse remodeling and improve long-term outcomes.

An alternative method for unloading areas of high wall stress is electrical preexcitation. Electrical preexcitation has previously been shown to modify, in the short term, the regional distribution of stroke work within the normal heart, reducing stroke work near the site of preexcitation and increasing stroke work in regions remote from it. Long-term cardiac pacing has been shown to redistribute muscle mass within the ventricle. Regions of the heart that are electrically activated first experience reduced preload and develop thinner walls, whereas late-activated regions experience increased preload and develop myocardial hypertrophy. These reported studies were performed on normal hearts without regional abnormalities such as those seen after MI. Recent clinical data suggest that long-term pacing starting 30 to 60 days after MI may attenuate ventricular remodeling. However, no studies exist that have assessed the mechanistic effects of preexcitation and regional unloading on short-term hemodynamics and long-term ventricular remodeling after acute MI.

We hypothesized that ventricular preexcitation near the MI would, in the short term, reduce mechanical loading in and around a myocardial infarct and that this would attenuate...
adverse LV remodeling and dysfunction in the long term. We tested the short-term and long-term hypotheses in porcine infarct models. In the short-term model, we demonstrated the effect of preexcitation on wall loading characteristics and studied the effects of pacing site and atrioventricular (AV) delay. In the long-term study, we evaluated the effects of long-term preexcitation on ventricular function and remodeling.

Methods

Animal Model

Myocardial infarcts comprising ~20% of the LV were induced in 24 male or female crossbred swine (Figure 1) by occlusion of the circumflex or left anterior descending coronary artery. Permanent coronary ligation or occlusion/reperfusion with angioplasty balloon catheters was used in separate animals. A ligation model was chosen for the long-term study because of its reliability in producing an infarct that is consistent in both size and location. In the short-term study, both ligation and balloon occlusion/reperfusion models were used. The occlusion/reperfusion model was chosen to demonstrate the feasibility of the therapy in a more clinically relevant setting. Twelve pigs weighing 45 to 65 kg were studied short term. Twelve additional pigs weighing 28 to 38 kg entered the 8-week long-term study. All animals used in the present study were treated in accordance with the National Institutes of Health “Guidelines for the Care and Use of Laboratory Animals.” The protocol was reviewed and approved by the Internal Animal Care and Usage Committees of Boston Scientific Corporation and the Minneapolis Veterans Administration Medical Center. An ear tag provided unique identification for each animal.

Procedures

Short-Term Mechanisms Study

A median sternotomy was performed, and 1 pacing lead (Guidant, St Paul, Minn; model 4458) was secured to the right atrium, with 3 leads (Guidant, model 4316) secured to the LV. The leads were positioned within the ischemic, nonischemic border, and remote regions. All leads were connected to an external automated pacing system (Flexstim II, Guidant). Sonomicrometry crystals (Sonometrics Inc, London, Ontario, Canada) were implanted in a specific spatial arrangement on the LV myocardium and were used to assess regional segmental strain, contractility, and stroke work. Recordings of aortic blood flow (Transonic Systems Inc, Ithaca, NY) and LV pressures (Millar Instruments, Houston, Tex) were measured simultaneously. All data were collected while the ventricle was stimulated in an atrial-triggered mode (VDD) according to a protocol composed of a random sequence of pacing sites and AV delays. The pacing AV delay was set at 75%, 50%, 25%, and 10% of the intrinsic PR interval. The LV was paced in the MI, border, or remote zones individually or from these multiple sites simultaneously. A steady state protocol was developed in which for each combination of site(s) and AV delay, the ventricle was paced for 60 beats followed by 60 beats of intrinsic rhythm.

Two animals had permanent left anterior descending coronary artery ligation and were studied on the day of the ligation. Another 3 animals had left circumflex coronary artery ligation and were also studied on the day of ligation. Animals that were studied on the same day as the MI had all data collected 1 to 6 hours after the MI. Seven animals had balloon occlusion/reperfusion. Three of these animals were studied 1 week after the MI, and 4 were studied 2 weeks after the MI (Figure 1).

Stroke work in a cardiac cycle was calculated with the following equation:

\[
Strain = \frac{(L - L_0)}{L_0}
\]

where \( L \) is the maximum segment length during the cardiac cycle, and \( L_0 \) is the segment length at a chamber pressure of zero. \( L_0 \) was computed as the x-intercept of the end-systolic pressure-length relation during transient vena caval occlusions. If the correlation coefficient for the end-systolic pressure-length relation was <0.80, \( L_0 \) was calculated in a different manner. In this case, segment length at end diastole was plotted as a function of LV end-diastolic pressure. \( L_0 \) was determined to be the y-intercept, the length at a chamber pressure of 0 mm Hg. It was typically necessary to use this second approach on segments with passive movement located in the MI region. Figure 2 illustrates the changes in pressure/segment loops during an inferior vena cava occlusion along with a graphical determination of \( L_0 \). Figure 2 also emphasizes the differences between contractions in the infarct, border, and remote regions.

Long-Term Study

Surgical Procedures

A left thoracotomy through the third intercostal space was performed to expose the left epicardial surface. An active-fixation bipolar endocardial lead (Guidant, model 4245) was sutured to the epicardial surface of the left atrial appendage. Two unipolar epicardial leads (Guidant, model 4316) were sutured in place on the LV. The tip of the first LV lead was implanted in a midanterior position near the left anterior descending coronary artery and ~2 cm inferior to the AV groove in the intended border region. The tip of the second LV lead

![Pacing Pre-excitation Study](image-url)
was implanted in a posterolateral position ∼2 cm inferior to the AV groove in the intended infarct region. Both LV leads were connected to a custom-made 2-into-1 “Y” adapter. The leads were connected to an implantable pulse generator (Guidant, Insignia model 1291). The origin of the left circumflex coronary artery was permanently ligated.

Any potentially lethal ventricular arrhythmias were treated with internal or external defibrillation. Animals were randomly assigned to either control or therapy arms. Therapy animals received pacing therapy in VDD mode at a shortened AV delay of 15 minutes after pacing was turned off. Doppler, M-mode, and 2D images were recorded. LV and atrial dimensions and the degree of mitral regurgitation were measured according to American Society of Echocardiography guidelines.21

Pathology

The animals were euthanized 56±3 days after MI, and hearts were excised and weighed. Six short-axis cross-sectional serial sections were made of the right ventricle and LV. Infarct size was determined by dividing the scar circumference by the total LV circumference and multiplying by the corresponding section thickness.

Apoptosis

Cardiac apoptosis was evaluated in the border areas of the LV by measuring the number of activated caspase–positive cells in myocardial sections stained by the Apologix carboxyfluorescin caspase-detection technique (Cell Technology, Minneapolis, Minn) as described previously.22 The activated caspase–detection technique has been validated to show in situ apoptosis. Slides were labeled for activated caspases and counterstained with hematoxylin and eosin. Cells positive for activated caspase were counted in 30 random fields in each of the animals. Laboratory personnel blinded to therapy performed the staining and counting. Myocyte origin of Apologix–positive apoptotic cells was confirmed by visualization of hematoxylin-and-eosin– and α-actin–stained paired slides under high power. Terminal dUTP nick end-labeling (TUNEL) staining was done with the TACS-XL Blue Label Kit (R&D Systems, Minneapolis, Minn).

In view of the problems associated with the primary use of TUNEL to define apoptosis, the Apologix technique was used as the primary measure of apoptosis, and TUNEL provided secondary validation of the trends in apoptosis.

Statistical Analysis

Descriptive values are expressed as mean±SD or SEM where noted. Separate repeated-measures ANOVAs (with Greenhouse-Geisser correction) with 2 repeated factors (3 locations and 4 AV delays), followed by simple linear contrasts with Bonferroni correction for multiple comparisons, were used to assess the effects of location and AV delays on percent change from no pacing in the border region strain and on cardiac output. Percent changes in regional strain, global stroke work, and global cardiac output across 4 AV delays were assessed by 1-way repeated-measures ANOVA, followed by between-delay Bonferroni-corrected paired comparisons. Long-term data were analyzed with Student unpaired t test to assess differences between therapy and control arms, and a paired t test was used to assess changes over time within each treatment group. For all tests, a P value less than 0.05 was considered statistically significant. SPSS software (version 14, SPSS Inc, Chicago, Ill) was used to perform all analyses.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Short-Term Mechanistic Study

Effect of Preexcitation on Regional Contraction Patterns

Figure 3 shows sonomicrometer displacement tracings from 1 representative animal with a posterolateral infarction. In these tracings, the pacing site and the parameters were identical to those used in the long-term study with an AV delay of 4 and Table 1. For both border-region strain and cardiac output, percent changes in regional strain, and on cardiac output. Percent changes in regional strain, global stroke work, and global cardiac output across 4 AV delays were assessed by 1-way repeated-measures ANOVA, followed by between-delay Bonferroni-corrected paired comparisons. Long-term data were analyzed with Student unpaired t test to assess differences between therapy and control arms, and a paired t test was used to assess changes over time within each treatment group. For all tests, a P value less than 0.05 was considered statistically significant. SPSS software (version 14, SPSS Inc, Chicago, Ill) was used to perform all analyses.

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output, significant main effects were found for AV delay ($P<0.001$). Cardiac output was least affected at the longest AV delay, whereas regional stroke work and strain decreased the most with the shortest AV delay. A compromise of achieving adequate regional work reduction without severely affecting cardiac output was attained at 50% AV delay. Note that at 50% AV delay (Figure 4), border-zone pacing reduced regional strain by $\approx 5\%$ while mildly affecting cardiac output.
Regional strain, cardiac output, and stroke work at an AV delay of 50% were significantly different from those at all other AV delays (Table 1).

**Effect of Preexcitation Site on Regional and Global Function**

Figure 4 also compares the effect of pacing at the 3 different sites (pacing from border or infarct single sites separately or from both simultaneously). For both border-region strain and cardiac output, significant main effects were found for preexcitation site \((P=0.007\) and \(P=0.01\), respectively). The pacing site and interval interaction was not significant for either outcome variable \((P=0.29\) for strain, \(P=0.11\) for cardiac output). Simple post hoc linear contrasts revealed that pacing from the infarct zone was significantly different than pacing from the infarct-and-border zones for regional strain \((P=0.03\) and for cardiac output \((P=0.03\), all comparisons Bonferroni-corrected). Border-region strain assessed while pacing from the infarct region was significantly different than from border-region pacing \((P=0.02\); however, these areas were not significantly different when cardiac output was assessed \((P=0.24). Border-region pacing was not significantly different from infarct-border pacing for border-region strain or cardiac output \((P=0.87\) and \(P=0.30\), respectively). Pacing from the border or border-and-infarct region reduced regional strain at AV delays of 50% or below; however, no effect was observed on regional strain in the border region when pacing from the infarct region at an AV delay of 50% of the intrinsic PR interval. Global cardiac output decreased progressively with decreasing AV delay.

**Long-Term Results**

**Effect of Preexcitation Therapy on Development of Post-MI Structural Remodeling**

Table 2 summarizes the main echocardiographic results in the therapy and control groups 2 days after MI and at the 8-week end of study. The 2 groups had similar characteristics at baseline. LV and left atrial size increased significantly from baseline to 8 weeks in both groups. Preexcitation therapy substantially reduced adverse ventricular remodeling. The increase in LV end-diastolic diameter was significantly smaller in therapy animals than in control animals \((0.9\pm 0.3\) versus \(1.5\pm 0.5\) cm, respectively, \(P<0.03\)). The degree of mitral regurgitation remained unchanged in the therapy group but increased significantly in the control group \((-0.42\pm 1.20\) versus \(1.67\pm 0.61\), \(P=0.004\)). Left atrial enlargement was significantly attenuated in the therapy group \((1.06\pm 0.78\) versus \(2.32\pm 0.88\) cm, \(P<0.04\)). Although interventricular septal thickness increased significantly in the paced group, it remained unchanged in the nonpaced group. Posterior wall thickness decreased significantly in control animals and was unchanged in therapy animals (Table 2).

The differences in remodeling were not attributable to differences in infarct size, because they were comparable between treatment and control arms (Table 3). Body weight at
TABLE 3. Body Weight, Heart Weight, Infarct Size, and Apoptotic Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=6)</th>
<th>Therapy (n=6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight at baseline, kg</td>
<td>33.1±3.94</td>
<td>30.0±2.30</td>
<td>0.1634</td>
</tr>
<tr>
<td>Body weight at the end of study, kg</td>
<td>65.3±3.20</td>
<td>65.0±5.40</td>
<td>0.9047</td>
</tr>
<tr>
<td>Infarct size, %</td>
<td>19.7±3.2</td>
<td>21.0±4.1</td>
<td>0.2814</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>359.6±29.3</td>
<td>319.8±20.8</td>
<td>0.0219</td>
</tr>
<tr>
<td>Heart weight/body weight, g/kg</td>
<td>5.52±0.49</td>
<td>4.93±0.24</td>
<td>0.0263</td>
</tr>
<tr>
<td>Heart weight/tibia length, g/cm</td>
<td>22.1±1.7</td>
<td>19.6±1.2</td>
<td>0.0200</td>
</tr>
<tr>
<td>No. of apoptotic cells*</td>
<td>46.3±30.1</td>
<td>33.0±7.0</td>
<td>0.1710</td>
</tr>
</tbody>
</table>

Data are reported as average and SD.

*A apoptotic cells were only assessed in 3 therapy animals and 6 control animals.

the beginning and the end of the study also was not significantly different between study groups. Heart weight was significantly lower in therapy animals than in control animals (319.8±20.8 versus 359.6±29.3 g, P=0.02), as were the ratios of heart weight to body weight and to tibia length (Table 3). Although not statistically significant, fewer myocardial apoptotic cells were found in the border region in therapy animals than in control animals (33.0±7.0 versus 46.3±30.1, P=0.171).

Discussion

The results of the present study have shown that LV preexcitation pacing at the border zone of a myocardial infarct can reduce mechanical loading characteristics of the infarct and border regions in the short term and, in the long term, attenuate adverse ventricular remodeling. We have also characterized the effect of pacing site and AV delay on regional and global function.

During the development of the normal heart, factors such as global ventricular geometry and wall thickness are controlled to normalize stress and strain and to maintain synchronous ventricular contraction. An infarct alters the balance between these factors, which results in hypertrophic signaling that may be the stimulus that leads to post-MI remodeling. High wall stress has also been shown to promote apoptosis and necrosis of myocytes, a process that is probably not reversible and further promotes adverse remodeling.

Therapies such as vasodilators, LV assist devices, and cardiac restraint devices have been shown to attenuate ventricular remodeling, which supports the concept that methods to unload areas of high wall stress may be useful in preventing ventricular remodeling. Electrical preexcitation has also been shown in other experiments to reduce local work and, presumably, preload, while increasing them in remote, late-activated regions. A study in patients 30 to 45 days after MI with reduced ejection fraction and narrow QRS suggests biventricular pacing attenuated LV dilation compared with a nonpaced group. The present animal data support these findings and suggest a possible mechanism for these beneficial effects. Using regional strain and stroke work to assess regional loading characteristics, we showed that pacing preexcitation can preferentially reduce these loading characteristics. Similar to the short-term data from the present study, previous studies using magnetic resonance imaging in normal hearts have shown that electrical preexcitation reduced local loading characteristics while increasing them in remote, late-activated regions. These experiments, however, were not performed in hearts with MI. It appears that wall loading may have been redistributed in animals in the present study from the MI site to the remote regions, as evidenced in the short term by an increase in stroke work in regions remote to the pacing site and in the long term by a slight increase in myocardial thickness in regions remote from the pacing site. This is supported by previous studies showing that pacing preexcitation can induce long-term changes in myocardial mass. Areas near the pacing site have a reduction in mechanical loading characteristics, whereas areas remote from the pacing site have increased loading characteristics. Therefore, a redistribution of mechanical stress on the heart is observed with preexcitation, which results in a relative decrease in LV mass in areas near the pacing site and hypertrophy in areas remote to the pacing site. Such long-term effects of pacing may have contributed to the beneficial effects in the present study evidenced by the significant increase in the interventricular septal thickness in therapy animals compared with the control group.

A number of possible mechanisms might underlie the reduction in heart weight and attenuation of LV and left atrial enlargement with preexcitation pacing seen in the present study. Remodeling of the ventricle, clinically manifested as changes in size, shape, and function of the heart after cardiac injury, is an important mechanism underlying the progression of heart failure. It is a process that is common to multiple causes of heart failure and that can be delayed or even reversed by appropriate treatment. Eccentric remodeling in the control animals was suggested in the present study by a higher magnitude of ventricular and left atrial enlargement associated with thinning of the infarct-related posterior wall and the overall increase in heart weight. It is now commonly recognized that progressive LV dysfunction occurs, and apoptosis contributes to this process. Although only a few animals were studied, a higher rate of apoptosis in the border region in the control animals was noted that was associated with a decrease in posterior wall thickness in these animals. Different loading conditions, particularly left atrial pressure and LV afterload, might conceivably be involved in the changes in LV and left atrial dimensions over time. In the present study, lower heart weight in paced animals was...
associated with attenuation of LV and left atrial enlargement, which suggests this was not likely to be related to filling conditions. The extent of mitral regurgitation is another important indicator of remodeling, especially in patients with posterior infarctions. The present data indicate that control animals had a significant increase in the degree of mitral regurgitation compared with therapy animals. Unloading strategies, such as with the use of ventricular restraint devices, have been shown to attenuate ischemic mitral regurgitation.

How preexcitation is applied is likely to be a critical factor in the delivery of successful therapy. High-stress areas must be sufficiently preexcited to be adequately unloaded. However, as demonstrated in Figure 4, excessive preexcitation, with AV delays <50% of the intrinsic PR interval, significantly impacted atrial transfer and reduced cardiac output. The AV delay chosen for therapy must be a compromise between regional LV unloading and maintenance of global function. Therefore, an AV delay of ~50% of the intrinsic PR interval was chosen for the long-term study, and this AV delay produced long-term benefit by attenuating ventricular remodeling.

The preexcitation site is also important in delivering therapy. As in previous studies in normal hearts, the greatest effect on unloading was in regions near the pacing site. Little additional benefit existed with multisite pacing over single-site pacing, except, perhaps, to maintain reliable capture. After MI, the infarct region undergoes remodeling that involves necrosis and fibrosis. The border region, under increased wall stress, may experience myocyte loss through apoptosis, wall thinning, and remodeling according to the well-characterized process of infarct expansion. Therefore, the border region is most likely the critical region for therapy to halt infarct expansion. These studies demonstrate that long-term preexcitation of the border and ischemic regions does attenuate remodeling.

This preliminary study has several limitations. LV remodeling was assessed with LV diameters and heart weight in the long-term study because volumetric analyses of transthoracic apical long-axis images were not performed owing to the difficulty in obtaining a usable echocardiographic window in pigs. Transthoracic parasternal short-axis imaging is much more reliable in this animal model. The individual echocardiographic measurements of LV cavity size were subject to multiple-measurement error. This error was minimized by the use of the same sonographer, equipment, and techniques for all echocardiograms. All images were analyzed by the same investigator, who was blinded to the animal’s randomization arm. Other volumetric techniques, such as MRI, could not be performed because of the pacemaker and leads. We were able to measure apoptosis in only 3 treated animals.

Ideally, the same animals would have been studied short term and long term; however, the rigorous and invasive nature of the short-term study, which included the use of 16 sonomicrometry crystals and an aortic flow probe, especially on rapidly growing animals, would most likely have affected survival and may have introduced additional error. Regional strain measurements were limited in resolution and locations owing to the limitations of the sonomicrometry implantation techniques. Strain within the septal region was not analyzed.

Although we did adjust for multiple comparisons where possible, we realize that the large number of comparisons needed to assess changes within and between groups may have led to an increased risk of type I error. Therefore, the conclusions drawn from the present study should be viewed as suggestive in nature and may require that additional testing be performed to confirm the significance of these results.

Conclusions

In the short term, electrical preexcitation near an infarct reduces wall loading in the injured regions. The extent of reduction in regional wall loading and cardiac output is dependent on both pacing site and AV delay. Long-term preexcitation in the border region at an AV delay that balances reduction in regional strain and maintenance of cardiac output attenuates adverse remodeling over time. Further clinical studies will be needed to expand these observations.

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Disclosures

A.C. Shuros, Dr Salo, and Dr Pastore have ownership interest in Boston Scientific and are employed by Boston Scientific. Drs Chandrashekar and Anand have received honorary and grant funding from Boston Scientific. Drs Florea and Kuskowski report no conflicts.

References


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