Cardiac Support Device Modifies Left Ventricular Geometry and Myocardial Structure After Myocardial Infarction

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Background—Whether mechanical restraint of the left ventricle (LV) can influence remodeling after myocardial infarction (MI) remains poorly understood. This study surgically placed a cardiac support device (CSD) over the entire LV and examined LV and myocyte geometry and function after MI.

Methods and Results—Post-MI sheep (35 to 45 kg; MI size, 23±2%) were randomized to placement of the CorCap CSD (Acorn Cardiovascular, Inc) (MI+CSD; n=6) or remained untreated (MI only; n=5). Uninstrumented sheep (n=10) served as controls. At 3 months after MI, LV end-diastolic volume (by MRI) was increased in the MI only group compared with controls (98±8 versus 43±4 mL; P<0.05). In the MI+CSD group, LV end-diastolic volume was lower than MI only values (56±7 mL; P<0.05) but remained higher than controls (P<0.05). Isolated LV myocyte shortening velocity was reduced by 35% from control values ($P<0.05$) in both MI groups. LV myocyte β-adrenergic response was reduced with MI but normalized in the MI+CSD group. LV myocyte length increased in the MI group and was reduced in the MI+CSD group. Relative collagen content was increased and matrix metalloproteinase-9 was decreased within the MI border region of the CSD group.

Conclusions—A CSD beneficially modified LV and myocyte remodeling after MI through both cellular and extracellular mechanisms. These findings provide evidence that nonpharmacological strategies can interrupt adverse LV remodeling after MI. (Circulation. 2005;112:1274-1283.)

Key Words: collagen ■ contractility ■ myocardial infarction ■ matrix metalloproteinases ■ heart-assist device

Left ventricular (LV) remodeling subsequent to myocardial infarction (MI) is characterized by dilatation and progressive dysfunction and is associated with an increased risk of heart failure.1-3 Recent surgical interventions that putatively modify wall stress patterns have demonstrated favorable effects on LV remodeling after MI.4-7 For example, initial studies have demonstrated that the placement of a polyester-weave device around the heart, called a CorCap Cardiac Support Device (CSD; Acorn Cardiovascular, Inc), favorably reduced LV dilation in an acute sheep model of MI.7 However, the precise cellular and extracellular events associated with these effects on LV geometry remain unclear. The overall goal of the present study was to address potential cellular and extracellular constituents that may be affected by CSD placement after MI. Because the myocyte is the fundamental contractile unit of the heart, the first objective of the present study was to measure isolated LV myocyte function and geometry after MI in sheep with and without CSD placement.

Recent studies of the mechanisms of post-MI remodeling indicate that a family of proteolytic enzymes, the matrix metalloproteinases (MMPs), contribute significantly to LV remodeling.8-14 Endogenous MMP activity is controlled by the tissue inhibitors of metalloproteinases (TIMPs).9-12 Past basic and clinical studies have demonstrated alterations in MMP and TIMP profiles, providing evidence for a direct relationship between MMP induction and the post-MI myocardial remodeling process.8-17 Accordingly, the second objective of this study was to examine the effects of CSD placement on the post-MI myocardial matrix and MMP and TIMP levels.

Myocardial remodeling after MI results in the recruitment and transformation of a number of cell types within the infarct region and the viable remote myocardium. Of note, the fibroblast, which is the highest-density cell type within the myocardium, undergoes phenotypic transformation into a more contractile cell type called the myofibroblast.18-21 The myofibroblasts express de novo levels of the contractile protein α-smooth muscle actin, which is a defining feature of
Medical University of South Carolina.

Use committees of both the University of Pennsylvania and the National Institutes of Health (NIH publication 86-23, revised 1996), Guide for Care and Use of Laboratory Animals

These transformed fibroblasts. The signals that contribute to myofibroblast differentiation after MI are likely multifactorial, but mechanical stress mediated through the myocardial matrix likely plays a pivotal role. Because it has been demonstrated in past experimental studies that wall stress patterns may be altered with placement of the CSD, it can be hypothesized that the myocardial fibroblast phenotype may also be affected in the post-MI period. Thus, the final objective was to measure the relative density and distribution of myofibroblasts within the myocardium and within the CSD after MI.

Methods

Study Design

Dorsett hybrid sheep (male; weight, 30 to 40 kg) underwent MI induction to examine the effects of cardiac support device (CSD; CorCap Cardiac Support Device, Acorn Cardiovascular, Inc) placement on LV geometry and function after MI. Surgical placement of the CSD was performed at 7 days after MI induction. The rationale behind placing the CSD at 7 days after MI was 3-fold. First, this 7-day post-MI period allowed the acute infarction phase to subside.

Second, past studies have demonstrated that the degree of LV dilation is accelerated within the first 30 days after MI; therefore, strategies deployed within this time frame may attenuate this degree of MI expansion.

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Myocardial Sample Preparation

For the terminal studies, the sheep were anesthetized, and the hearts were extirpated. The LV free wall was separated, and myocardial samples from the remote, border, peri-infarct, and MI regions were obtained as shown in Figure 1. In addition, a coronal section was used to determine MI size by triphenyltetrazolium staining. The obtuse marginal branch of the circumflex coronary artery was cannulated and used to isolate myocytes as described previously.

The liberated LV myocytes were plated onto coverslips for myocyte function studies. An aliquot of the isolated myocytes was fixed in a buffered formalin solution and prepared for morphometric studies.

Myocyte Function

Myocyte contractile function was determined by well-described techniques. Contractile function data for each myocyte were recorded from a minimum of 20 consecutive contractions. After collection of baseline indexes of myocyte function, measurements were then performed in the presence of 25 mmol/L (-)-isoproterenol.

Histomorphometry, Immunohistochemistry, and Collagen Biochemistry

Formalin-fixed myocardial sections from each region were stained with either hematoxylin and eosin (H&E) or picrosiris red. From the H&E-stained sections, images were digitized to determine cross-sectional areas (ImagePro version 4.0, Media Cybernetics). From the picrosiris red–stained sections, percent fibrillar collagen staining was computed (ImagePro). LV myocardial sections were stained for α-smooth muscle actin (1:200 dilution, A2547, Sigma Chemical Co) as described previously. Positive staining for α-smooth muscle actin was visualized and quantified (ImagePro). The histomorphometric measurements were taken from within the midmyocardium for each sample to avoid cutting and crush artifacts.

Figure 1. A, MI was induced by permanent ligation of major diagonals (D1, D2, D3, D4) of left anterior descending (LAD) coronary artery. Borders of infarcted myocardium were identified, and radiopaque markers (M) were sutured around periphery of identified region. B, Schematic depicting myocardial sampling algorithm used. Second obtuse marginal (OM2) artery of circumflex coronary artery that perfused remote and border regions on LV was identified, cannulated, and used for myocyte isolation. Border region was defined as section extending from edge of MI toward remote, viable myocardium. Peri-infarct region was defined as section extending from MI border toward center of MI region. Remote viable myocardium was obtained from posterior, non-MI LV free wall.

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Collagen content from each of the sampled full-thickness myocardial regions was quantified by measuring the amount of hydroxyproline with techniques previously described. In addition to the studies outlined above, block sections of the myocardium and CSD were formalin fixed in situ. Full-thickness samples were then subjected to routine H&E, picrosirius red, and immunohistochemistry α-smooth muscle actin as described above. In addition, sections were stained for fibroblast marker DDR-2 (1:250 dilution, GEA4023-1, Genex) and for the lymphocyte marker CD-4 (1:100 dilution, CBL127, Cedarlane). The specificity of the antibody for myocardial fibroblasts has been demonstrated previously.

**LV Myocardial MMP and TIMP Levels**

LV myocardial samples were prepared for zymographic studies as described previously. Thezymograms were digitized, and the size-fractionated banding pattern representing MMP proteolytic activity was converted to an integrated optical density (Gel Pro Analyzer, Media Cybernetics). Integrated optical density values obtained for the non-MI reference control samples were used to normalize the integrated optical density values obtained for the MI samples. Therefore, regional zymographic levels were expressed as a percentage of reference control values. The relative abundance of MMP-1, MMP-13, TIMP-1, and TIMP-4 was determined in the LV samples by immunoblotting.

The primary antisera (0.2 μg/mL anti–MMP-1 [M351], 0.2 μg/mL anti–MMP-9 [AB804], 0.25 μg/mL anti–MMP-13 [AB8114], 0.1 μg/mL anti–TIMP-1 [AB8116], 0.1 μg/mL anti–TIMP-4 [AB816], Chemicon or Oncogene) were confirmed to specifically react to the sheep protein of interest in initial blotting studies. Quantification of the immunoblots was performed in the same manner as the zymographic data.

**Data Analysis**

LV volume, MI size, and ejection fraction were compared by 1-way ANOVA. Myocyte volumes were computed as the product of LV volume, MI size, and ejection fraction were compared by 1-way ANOVA. Myocyte volumes for which contractile function was determined in Table 2. Nevertheless, statistical analyses were performed using the average regional measurements from each sheep. Resting myocyte length increased in the remote and border regions in the MI only group and normalized in the MI+CSD group. Myocyte percent and shortening velocity were reduced by ~35% in both MI groups. Myocyte inotropic response was examined by exposure to the β-adrenergic agonist isoproterenol; absolute values are summarized in Table 2. The relative β-adrenergic response, computed as a function of change from baseline values for the same myocyte, is summarized in Figure 2. The β-adrenergic response was reduced from control values in the MI only group but was normalized in the MI+CSD group.

**Myocyte Cross-Sectional Area and Volumes**

Myocyte cross-sectional area in the remote and border regions of both MI groups were higher than control values (Figure 3). Myocyte cross-sectional area in the remote region of the MI+CSD group was lower than that of the MI only group. Computed myocyte volumes from both MI groups were higher than control values. However, myocyte volumes were lower in the remote region of the MI+CSD group compared with MI only values.

**Myocardial Collagen**

Collagen content was increased in the MI region in both groups but was higher in the MI+CSD group (Figure 4). Moreover, relative collagen content was increased in the remote and border regions in the MI+CSD group. Hydroxyproline results yielded a similar trend. Hydroxyproline was increased in the peri-infarct and MI regions in both groups but was higher in the MI+CSD group.

**α-Smooth Muscle Actin Content**

Compared with control values, α-smooth muscle actin staining was increased in the border region of the MI only group.

### TABLE 1. LV Geometry and Function and MI Size After MI: Effects of a CSD

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MI Only</th>
<th>MI+CSD</th>
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<tr>
<td>In vivo measurements</td>
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<tr>
<td>End-diastolic volume, mL</td>
<td>43.0±3.7</td>
<td>98.2±8.3</td>
<td>56.3±7.0</td>
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<td>End-systolic volume, mL</td>
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<td>72.8±8.3</td>
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<td>Stroke volume, mL</td>
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<td>25.4±3.6</td>
<td>19.5±2.4</td>
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<tr>
<td>Ejection fraction, %</td>
<td>46.8±4.1</td>
<td>26.5±3.6</td>
<td>34.6±1.8</td>
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<tr>
<td>MI size, %</td>
<td>44%</td>
<td>10%</td>
<td>15%</td>
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<tr>
<td>Terminal measurements</td>
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<td></td>
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<tr>
<td>Right ventricular weight, g</td>
<td>33.8±1.5</td>
<td>57.9±8.1</td>
<td>67.2±4.6</td>
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<tr>
<td>LV+septum weight, g</td>
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<td>243.4±17.4</td>
<td>225.7±12.1</td>
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<tr>
<td>LV weight/body weight, g/kg</td>
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<td>5.1±0.2</td>
<td>5.1±0.3</td>
</tr>
<tr>
<td>Sample size, n</td>
<td>10</td>
<td>5</td>
<td>6</td>
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Values are presented as mean±SEM. *Compared as a function of an LV coronary sectional area. †P<0.05 vs control, ‡P<0.05 vs MI only.
and the peri-infarct region of the MI+CSD group (Figures 5 and 6). In the border region of the MI+CSD group, α-smooth muscle actin content was lower than in the MI only group.

Full-block in situ sections of the myocardium and CSD were subjected to histochemical analysis. Representative photomicrographs are shown in Figure 6. H&E staining revealed a clear interface between the epicardium and the CSD in that an infiltrating fibrosis or inflammatory process was absent. However, the polyester fibers of the CSD were significantly enshrouded within a highly organized matrix containing a high density of cells. Collagen staining of the CSD sections revealed a highly organized fibrillar matrix spiraling around individual fibers of the CSD in both a circumferential and a longitudinal orientation (Figure 6c and 6d). Immunohistochemical staining for CD-4, a pan-lymphocyte marker, was negative in multiple sections (minimum of 4) taken from each CSD-implemented sheep (data not shown). Thus, these cells were not associated with chronic inflammation. However, a number of the cells stained positive for DDR-2, suggesting that the cells contained within the CSD were likely of fibroblast origin (data not shown).25 Robust staining for α-smooth muscle actin was localized to these cells contained within the CSD (Figure 6e and 6f), consistent with myofibroblasts.19–21

**MMP and TIMP Myocardial Levels**

Quantitative immunoblotting for MMP and TIMP species was performed for each region in the post-MI groups and compared with referenced control values. Representative immunoblots are shown in Figure 7, and quantitative results are summarized in Figure 8. A distinct pattern of MMP/TIMP levels was observed in the post-MI samples. MMP-1 levels were reduced within the MI region, whereas MMP-13 levels increased in the opposite direction. In the MI+CSD group, MMP-1 levels were lower in the peri-infarct region compared with MI only values. MMP-13 levels were higher in the peri-infarct and infarct regions compared with MI only values. MMP-2 levels were increased in the peri-infarct, border, and infarct regions in both MI groups. MMP-2 levels tended to be higher in the MI+CSD group compared with MI only values. Immunopositive MMP-9 signals were detected in all myocardial samples and were reduced in the MI only group within the peri-infarct region. MMP-9 levels were reduced in the remote, border, and peri-infarct regions in the MI+CSD group. Within the MI region, TIMP levels were uniformly decreased in both MI groups. In the MI+CSD group, TIMP-1 levels were also reduced from control values within the remote, border, and peri-infarct regions. TIMP-4 levels were lower within the peri-infarct region of the MI+CSD group compared with the MI only group.

**Discussion**

Past pharmacological and surgical interventions have clearly demonstrated that reducing the extent of LV remodeling after MI has favorable effects on LV geometry and patient survival.3,26,27 Recently, animal studies using mechanical restraint have demonstrated favorable effects on post-MI remodeling.4–7 However, the cellular and extracellular events associated with these changes in post-MI remodeling remained to be established. The present study used an ovine post-MI model, deployed a CSD, and examined LV myocyte and extracellular matrix (ECM) structure. The significant findings of this study were 3-fold. First, CSD deployment after an established MI reduced LV dilatation; that reduction was paralleled by a reduction in isolated LV myocyte length and volumes. Second, post-MI CSD improved LV ejection fraction and myocyte inotropic response. Third, post-MI CSD increased collagen formation within the vulnerable regions of the MI and modified an important ECM proteolytic pathway (MMPs and TIMPs). These unique results...
demonstrated that placement of a CSD beneficially modified LV remodeling after MI by affecting both cellular and extracellular processes.

This study is the first to examine the effects of CSD placement on cellular and extracellular events after MI. Past studies have examined the effects on post-MI remodeling through placement of a mesh patch onto the region of the MI.\(^4\)\(^5\) In these studies, the mesh was placed before MI induction; therefore, regional restraint was operative before myocardial injury and remodeling. Nevertheless, these past studies provided evidence that myocardial restraint reduced the relative degree of MI expansion and altered relative fibrillar collagen levels within the border region.\(^4\) This laboratory has demonstrated previously that placement of the CSD in this ovine model of MI reduced the degree of regional akinesis and favorably affected myocardial energetics.\(^6\)\(^7\) Although these past studies did not directly quantify the cellular and/or extracellular bases for the improvement in regional myocardial geometry and function, it did provide the basis for generating the hypothesis that was tested in the present study. Specifically, we anticipated that placement of the CSD after MI would improve myocyte function and ECM structure and that the summation of these effects would translate into an improvement in LV geometry and function. Through isolated myocyte function studies and measurement of ECM composition and degradation pathways, the results from the present study provided direct evidence to confirm this hypothesis.

Past studies have clearly demonstrated that isolated myocyte remodeling occurs after MI and contributes to the changes in LV geometry.\(^28\)\(^29\)\(^30\) The present study demonstrated that in a large animal model of post-MI remodeling, isolated myocyte length and volumes increased within remote and border regions after MI. With the CSD placement after MI, isolated myocyte length and volumes were reduced from MI only values. The probable cause was that the mechanical forces driving the myocyte remodeling process were attenuated after placement of the CSD. However, myocyte geometry was not normalized with the CSD, probably because the CSD was placed at 7 days after MI and thus significant myocyte remodeling likely occurred before CSD placement. Nevertheless, what is important from this aspect of the study was that the reduction in LV volumes that occurred with CSD placement was paralleled by a reduction in myocyte length and volumes. This relative attenuation in myocyte remodeling after MI is comparable to that observed with specific pharmacological strategies such as interruption of the angiotensin receptor pathway.\(^31\) Thus, future studies to examine the potential additive effects of pharmacological treatment and
mechanical support such as a CSD in the post-MI setting would be warranted.

In the present study, contractile function was impaired in myocytes harvested from both the remote and border zones at 3 months after MI. These defects in myocyte contractility persisted in the CSD group. These findings suggest that the mechanism for the improvement in LV ejection performance was not due to an intrinsic improvement in contractile function but rather to improvements in the translation of myocyte shortening to overall LV pump function. Moreover, preservation of the ECM likely facilitated an improvement in the coordination of myocyte shortening into an increased efficiency of myocardial segment shortening. Indeed, a past study demonstrated regional improvements in myocardial segmental shortening after placement of the CSD after MI.6 Isolated myocyte inotropic response, as assessed by β-adrenergic receptor stimulation, was significantly impaired after MI. It has been demonstrated previously that defects in the excitation-contraction coupling process occur after MI.30 In addition, it has been reported that myocardial β-adrenergic receptor density is reduced after MI.32 Thus, the reduction in myocyte inotropic response observed after MI was likely due to both defects in excitation-contraction coupling and diminished β-receptor density. Myocyte β-adrenergic response was improved by placement of the CSD after MI. The basis for this effect is likely multifactorial, including increased β-receptor density and improvements in the excitation-contraction coupling process. From the findings from this study, future studies that more carefully examine the mechanisms for the improvement in myocyte inotropic response with placement of a CSD after MI are warranted.

In the present study, placement of the CSD clearly modulated important extracellular determinants of myocardial remodeling after MI. Specifically, the CSD retarded the degree of fibrillar collagen degradation in the peri-infarct region. The peri-infarct region is susceptible to collagen degradation and infarct expansion. Therefore, the relative preservation of fibrillar collagen in...
this region is likely responsible for attenuating the degree of post-MI LV dilation observed with the CSD. Moreover, placement of the CSD stabilized the collagen matrix within the MI and peri-infarct regions to a greater degree and likely facilitated the wound healing response and maturation of the infarct scar. Potential mechanisms for this favorable effect on collagen matrix formation and wound healing include the relative influence of the MMP/TIMP system and the effect of a reduction in the number of secretory myofibroblasts in the border region. The relative stoichiometric changes that occurred with respect to the MMP/TIMP profiles with the CSD suggest that the favorable effects on cellular and extracellular structure and function were due to the effects on this important myocardial proteolytic system. The rationale for choosing the MMP and TIMP types to be measured for this study was that the expression of these MMPs/TIMPs has previously been demonstrated to be altered in LV remodeling associated with human heart failure.9 In addition, a past study using a sheep MI model demonstrated region-specific changes in MMP and TIMP profiles.11 Similar directional changes in MMP/TIMP profiles occurred in the present study. For example, MMP-13 and MMP-2 levels increased within the MI regions, and TIMP levels were decreased. These changes would favor ECM remodeling and turnover. It has been demonstrated previously in a murine model that MMP-9 plays an important role in post-MI remodeling.14 In the CSD group, relative MMP-9 levels were reduced compared with MI only values. An important source of MMP-9 is inflammatory cells, suggesting that CSD placement altered the inflammatory response in the later post-MI period. This reduction in MMP-9 may also have contributed to the relative increase in collagen content within the MI and border regions with CSD placement. It has been recognized that a number of transcriptional and posttranslational regulatory steps determine MMP proteolytic activity. One important regulatory step is inhibition of active MMPs by TIMPs. Placement of the CSD did not normalize TIMP levels, suggesting that continued disparities in MMP/TIMP stoichiometry occurred in this post-MI model. It remains unclear from the present study what the long-term effects CSD placement may have on ECM structure and on the MMP/TIMP system. Nevertheless, the present study demonstrated that CSD placement after MI increased ECM content within the vulnerable border region and likely prevented further MI expansion.

The present study examined the relative expression of α-smooth muscle actin within the different myocardial regions

Figure 5. Left, Representative α-smooth muscle actin staining of LV myocardial sections obtained from border, peri-infarct, and MI regions of MI only and MI+CSD. Right, These immunostained sections were quantified for α-smooth muscle actin. Relative abundance for α-smooth muscle actin was highest in border region of MI only group. Relative α-smooth muscle actin was reduced in MI+CSD group. *P<0.05 vs control, †P<0.05 vs MI only, §P<0.05 vs border region. Scale bars=50 μm.
after MI. Robust staining for α-smooth muscle actin staining was observed within the border region after MI, which was reduced with the CSD. A phenotypic change in fibroblasts occurs after MI, particularly in viable myocardium adjacent to the infarct region, yielding a myofibroblast phenotype. Notably, these myofibroblasts express α-smooth muscle actin and can contribute to changes in matrix structure and function. It has been demonstrated that fibroblast transformation and expression of α-smooth muscle actin depend mechanical stress. CSD placement in a canine model of cardiomyopathy was associated with a reduction in stretch-response protein expression. Thus, placement of the CSD after MI most likely altered myocardial stress patterns, which in turn would modify this fibroblast phenotypic transformation. However, α-smooth muscle actin staining also occurs within the vascular component and can be reflective of the degree of vascularization. Within the peri-infarct and MI regions, greater vascularity and a relative increase in α-smooth muscle actin were observed with the CSD. These results suggest that using the CSD did not impair post-MI angiogenesis. Future studies that more carefully examine the biological behavior of the myofibroblasts and myocardial blood flow patterns after MI without and with the CSD are warranted.

Although the favorable effects of CSD placement after MI with respect to LV remodeling were likely attained through providing passive myocardial restraint, the biological basis by which the CSD exerted these effects remains poorly understood. Past studies have demonstrated that CSD placement does not impair passive filling properties of the LV and therefore allows normal deformation to occur during the cardiac cycle. Thus, the cellular and extracellular constituents contained within the CSD with chronic placement may be important in imparting the biophysical framework by which this device favorably modifies LV remodeling after MI. The present study began to address this issue by performing initial histochemical studies on the myocardial-CSD interface and the CSD itself after a 3-month placement in post-MI sheep. Within the viable myocardium, a clear epicardial-CSD interface could be readily appreciated, suggesting that a severe fibrotic/adhesive reaction did not occur.

**Figure 6.** Representative photomicrographs of full-thickness, in situ sections taken from remote region with respect to MI (as shown in Figure 1) demonstrating interface between epicardium (EPI) and CSD. a, Low-power image of H&E section demonstrating clear, definable interface between EPI and CSD. b, High-power image of H&E section revealed high density of cells with abundant ECM surrounding polyester fibers (arrows) of CSD. c, Low-power photomicrograph after picrosirius staining revealing increased matrix accumulation within CSD that did not traverse into EPI region. d, High-power image after picrosirius staining revealing abundant matrix formation surrounding fibers of CSD (arrows). e, Low-power photomicrograph after immunohistochemical localization for α-smooth muscle actin. Positive staining for α-smooth muscle actin within EPI region was localized to vasculature. Robust staining for α-smooth muscle actin was observed within CSD. f, High-power photomicrograph revealing clear localization of α-smooth muscle actin in cells surrounding fibers of CSD (arrows). Original magnification: a, c, e, ×10; b, d, f, ×40.

**Figure 7.** Representative immunoblots or zymograms for post-MI abundance of collagenases (MMP-1, MMP-13), gelatinases (MMP-2, MMP-9), and TIMPs (TIMP-1, TIMP-4) with (MI + CSD) or without (MI only) CSD. C indicates control; R, remote region; B, border region; P, peri-infarct region; and M, MI region.
between the epicardial surface and the CSD. Past studies demonstrated a similar finding after chronic placement of the CSD in dogs with microembolization-induced heart failure. In the present study, hypercellularity was noted within the CSD after chronic placement, but these resident cells were not of an inflammatory phenotype. Rather, increased myofibroblast cell density was observed within the CSD as evidenced by robust α-smooth muscle actin expression. Myofibroblasts have clearly been demonstrated to produce contractile force, and this force generation is mediated through engagement to the ECM. Significant matrix accumulation was observed surrounding individual CSD fibers that appeared to be of a highly organized nature. Thus, incorporation of contractile cells such as myofibroblasts and the synthesis of specific matrix components within the CSD are likely contributory factors by which this device may modify LV geometry after MI. However, this issue remains speculative and fell beyond the scope of the present study. The observations presented here support future mechanistic studies to elucidate the cellular and extracellular bases for the biophysical properties of the chronically placed CSD and to determine how they may operate within the context of post-MI remodeling.

In summary, the present study was the first to perform an integrative study into the cellular and extracellular changes that occur after deployment of a CSD after MI. Placement of this device modified the rate of LV dilation, improved myocyte geometry and inotropic responsiveness, and modified important determinants of matrix remodeling and wound healing. These cellular and extracellular effects were demonstrable when the CSD was placed after the acute MI period (7 days after MI), which holds great clinical relevance. However, further basic and clinical research is necessary to establish the role for surgical placement of CSDs in the treatment paradigm for patients after MI.

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