Attenuation of Left Ventricular Adverse Remodeling With Epicardial Patching After Myocardial Infarction

SONG-YAN LIAO, MD,1 CHUNG-WAH SIU, MBBS,1,2 YUAN LIU, MD,1 YUELIN ZHANG, MPHIL,1 WING-SZE CHAN, MBBS,1 ED X. WU, PhD,3 YIN WU, PhD,3 JOHN M. NICHOLLS, MBBS,4 RONALD A. LI, PhD,1,2 MICHAEL E. BENSER, PhD,5 STUART P. ROSENBERG, MS,5 EULJOON PARK, PhD,5 CHU-PAK LAU, MD,1 AND HUNG-FAT TSE, MD, PhD1,2

Hong Kong; Sylmar, California

ABSTRACT

Background: Previous studies suggested that epicardial patch applied to the infarcted site after acute myocardial infarction (MI) can alleviate left ventricular (LV) remodeling and improve cardiac performance; however, the effects of regional epicardial patch on chronic phase of LV remodeling remain unclear.

Methods and Results: We studied 20 pigs with MI induced by distal embolization and impaired LV ejection fraction (LVEF < 45%) as detected by gadolinium-enhanced cardiac magnetic resonance imaging (MRI). Eight weeks post-MI, all animal underwent open chest procedure for sham surgery (control, n = 12) or patch implantation over the infarcted lateral LV wall (patch group, n = 12). In the patch group, +dP/dt increased and LV end-diastolic pressure decreased at 20 weeks compared with immediately post-MI and at 8 weeks (P < .05), but not in the control group (P > .05). As determined by cardiac MRI, LV end-diastolic and end-systolic volumes increased at 20 weeks compared with 8 weeks in both groups (P < .05). However, the increase in LV end-diastolic volume (+14.1 ± 1.8% vs. +6.6 ± 2.1%, P = .015) and LV end-systolic volume (+12.1 ± 2.4% vs. −4.7 ± 3.7%, P = .0015) were significantly greater in the control group compared with the patch group. Furthermore, the percentage increase in LVEF (+17.3 ± 4.9% vs. +4.1 ± 3.9%, P = .048) from 8 to 20 weeks was significantly greater in the patch group compared with the control group. Histological examination showed that LV wall thickness at the infarct region and adjacent peri-infarct regions were significantly greater in the patch group compared with the control group (P < .05).

Conclusion: Regional application of a simple, passive synthetic epicardial patch increased LV wall thickness at the infarct region, attenuated LV dilation, and improved LVEF and +dP/dt in a large animal model of MI. (J Cardiac Fail 2010;16:590–598)

Key Words: Epicardial patch, myocardial infarction, ventricular remodeling.
alleviate LV remodeling and improve cardiac performance. Nevertheless, the effects of this type of regional restraint therapy on LV remodeling during the chronic phase of healing infarcts remains unclear. Therefore, the objective of this study was to investigate the effects of implanting an epicardial patch in a porcine model of chronic MI on LV remodeling and cardiac performance.

Methods

Animal Model of MI

Female pigs weighing between 45 and 50 kg were used for this study (n = 36). All animals were anesthetized with tiletamine and zolazepam (Zoletil 20 mg/kg intramuscularly). Endotracheal intubation was performed, and anesthesia was maintained with isoflurane (1.5% to 2.0%) and oxygen while the animals were mechanically ventilated. Coronary angiography was performed through a 6F JR4 guiding catheter (Cordis Corp, Miami, FL) via a right femoral artery cutdown. The left circumflex coronary artery distal to the first obtusus was occluded with balloon inflation and 700 microspheres were injected to generate MI as described previously. During the procedure, LV pressure was monitored to ensure at least 50% reduction in dP/dt after MI (Fig. 1A). The surface electrocardiogram and arterial blood pressure were continuously monitored throughout the procedure. All animals received amiodarone (300 mg intravenously over 1 hour) and lidocaine (100 mg intravenous bolus) before infarction to prevent or treat ventricular arrhythmias. All animal experiments conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health and was approved by the local institutional ethics committee for animal research.

Study Protocol

Eight weeks after MI, animals with evidence of MI and LV ejection fraction (LVEF) <45% on cardiac magnetic resonance imaging (MRI) were randomly assigned to receive either a sham open chest procedure (control group) or an epicardial patch implantation onto the infarcted region (patch group). Under general anesthesia and aseptic conditions, animals underwent left thoracotomy and pericardiotomy to expose the infarcted lateral wall (Fig. 1B). The infarcted region was easily identified on examination by pink discoloration and myocardial thinning. In the patch group, the patch was secured against the lateral infarcted myocardium with a single central helical tack, and the pericardiotomy was closed by 5-0 polypropylene suture. For the control group, the thoracotomy and pericardiotomy were similarly performed, but closed with no patch.

All animals underwent serial invasive measurement of LV hemodynamics using a micromanometer catheter (Millar Instruments, Houston, TX); during and immediately after MI induction, 8 weeks post-MI during the patch placement or sham operation, and 20 weeks post-MI during the long-term evaluation of cardiac performance.

Synthetic Epicardial Patch

A commercially available synthetic mesh composed of 2 layers of different materials was used (Bard Composix E/X Mesh, BARD Nordic, Helsingborg, Sweden). The first layer consists of a porous low-profile, large-pore polypropylene mesh and was placed in contact with the epicardium to provide optimal tissue ingrowth. The second layer is composed of sub-micronic expanded polytetrafluoroethylene and was placed toward the pericardium to minimize the risk of pericardial adhesions. The patch material was sized to a 52 mm × 72 mm ellipse and held together at its periphery with polyester suture covered with barium sulfate–impregnated medical adhesive to allow radiographic visualization (Fig. 1C). The patches were sterilized with ethylene oxide gas before implantation.

Cardiac MRI

Cardiac MRI examination was conducted with a Philips 3T Achieva scanner (Philips Medical System; Best, Netherlands). All the animals underwent cardiac MRI examination twice: 8 weeks post-MI and 20 weeks post-MI (12 weeks after patch/sham) (Fig. 2). During imaging, each pig was anesthetized with propofol and the heart rates ranged from 70 to 100 beats/min. Respiration was maintained by a ventilator, with breath-holding achieved by stopping the ventilator temporarily. A breath-hold balanced fast field echo cine sequence was first performed to acquire 8 short-axis slices covering the whole heart for evaluation of LV function. The sequence parameters were as follows: repetition time/echo time = 5.5/2.2 ms, cardiac frames = 20, slice thickness = 8 mm without slice gap, in-plane resolution = 1.04 × 1.04 mm², and acquisition time approximately 1 minute. Then, a bolus of a gadolinium contrast agent (gadopentetate dimeglumine, 0.5 mol/L, Magnevist, Germany) at a dose of 0.1 mmol/kg was injected intravenously. Breath-hold delay-enhanced T1-weighted imaging was carried out about 10 minutes later at the same 8 slice locations using an inversion recovery M2D-fast field echo sequence to investigate the myocardium viability, infarct location and volume. The parameters were repetition time/echo time = 3.8/1.3 ms, inversion recovery time = 275 ms, in-plane resolution = 0.68 × 0.68 mm², and acquisition time approximately 5 minutes.

Cardiac MRI Analysis

All images were reviewed and analyzed offline with specialized postprocessing software (Cinetool version 3.9.8, General Electric Healthcare Milwaukee, WI) by 2 investigators (W.S.C., W.Y.). Although the presence of the patch could not be blinded, the investigators performed all the analyses and interpretation of MRI imaging data in random order without any knowledge on the identity of the animals. The LV volume measurement, calculation of LVEF, and regional wall thickening were based on previously validated techniques. The LV volumes were determined by planimetry at the end-systolic and end-diastolic frames, and the LV myocardial mass was calculated by subtracting the endocardial volume from the epicardial volume at end diastole and then multiplying by the tissue density (1.05 g/mL).

Histology

After the long-term cardiac performance assessment 20 weeks post-MI, all pigs were anesthetized and the heart was exposed and arrested by injection of 100 mmol/l KCl solution. LV tissue samples were serially sectioned at 1 cm thickness in the LV transverse direction. Portions of the slices that contained infarcted myocardium were selected, from which approximate 1 cm² pieces within, adjacent, and remote to the infarct sites were sectioned to measure wall thickness. The tissues were then embedded in paraffin, sectioned into 5-µm slices and stained with Masson’s trichrome for histological examination. For detection of matrix metalloproteinase 9 (MMP-9), sections were successfully incubated (120 minutes,
Fig. 1. (A). Animal model of myocardial infarction and heart failure induced by left circumflex artery (LCX) coronary embolization. Upper panels show coronary angiogram of left anterior descending artery (LAD) and LCX before (left) and after (right) coronary embolization. Lower panels showed left ventricular pressure recording with the measurement of dP/dt before (left) and after (right) coronary embolization. (B) Photographs of the patch location at the lateral wall of left ventricle during the surgical procedure (left panel) and postmortem examination (right panel). (C) Photograph of the ellipsoid shape epicardial patch made of dual-layers of synthetic materials (left panel: polypropylene mesh; right panel: expanded polytetrafluoroethylene).
Results

Mortality and Morbidity

Twenty-six of 36 pigs with documented MI and impaired LVEF ≤45% on cardiac MRI were included in the study and randomized to receive either a sham open chest procedure (control group, n = 13) or epicardial patch implanta-
tion onto the infarcted region (patch group, n = 13). There was no significant difference in the percentage of infarcted myocardium as measured by delayed enhancement MRI imaging between the control group and the patch group (15 ± 2% vs. 16 ± 3%, P = .78). Three animals from each group died suddenly within 1 week after surgery. As a result, 10 animals from patch group and 10 animals from control group survived after the surgical procedure and completed the study protocol.

LV Hemodynamic Changes

In the control group, +dP/dt (796.9 ± 54.3 mm Hg/second vs. 1196.0 ± 117.0 mm Hg/second; P < .001), −dP/dt (556.9 ± 60.46 mm Hg/second vs. 844.4 ± 83.1 mm Hg/second; P < .001), and peak LV systolic pressure (79.1 ± 6.2 mm Hg vs. 103.5 ± 6.3 mm Hg; P < .001) significantly decreased and LV end-diastolic pressure (32.2 ± 2.3 mm Hg vs. 6.9 ± 1.5 mm Hg; P < .001) increased immediately post-MI compared with pre-MI. Similarly, in the patch group, +dP/dt (841.8 ± 79.0 mm Hg/second vs. 1303.0 ± 118.7 mm Hg/second, P < .001), −dP/dt (577.8 ± 54.3 mm Hg/second vs. 909.0 ± 38.1 mm Hg/second, P < .001), and peak LV systolic pressure (80.7 ± 4.3 mm Hg vs. 105.4 ± 4.1 mm Hg, P < .001) significantly decreased and LV end-diastolic pressure (31.8 ± 2.9 mm Hg vs. 6.8 ± 1.8 mm Hg, P < .001) increased immediately post-MI compared with pre-MI. Nevertheless, there were no significant differences in +dP/dt, −dP/dt, peak LV systolic pressure, and LV end-diastolic pressure between control group and patch group at either pre-MI or post-MI (Fig. 3A-D, P > .05).

In the control group, there were no significant differences in +dP/dt, peak LV systolic pressure, and LV end-diastolic pressure at 20 weeks compared with immediately post-MI and at 8 weeks (Fig. 3A-D, P > .05). In contrast, +dP/dt increased and LV end-diastolic pressure decreased in the patch group at 20 weeks compared with immediately post-MI (Fig. 3A, D, P < .05). In both the control and patch groups, −dP/dt significantly increased at 20 weeks as compared with post-MI (Fig. 3B, P < .05), suggestive of interval improvement in LV diastolic function.

Cardiac MRI

At 8 weeks, there were no significant differences in the LV end-diastolic volume (96.5 ± 2.8 mL vs. 97.7 ± 1.9 mL; P = .71), LV end-systolic volume (62.0 ± 2.6 mL vs. 61.3 ± 1.6 mL; P = .81), and LVEF (35.7 ± 1.7% vs. 37.2 ± 1.5%; P = .52) between the control group and patch group (Fig. 4A-C). In the control group, the LV end-diastolic volume (109.9 ± 2.7 mL, P < .001) and LV end-systolic volume (69.3 ± 2.5 mL, P = .0011) increased, but LVEF remained unchanged (36.9 ± 1.7%, P = .39) at 20 weeks as compared with 8 weeks (Fig. 4A-C, P < .05). In the patch group, the LV end-diastolic volume (104.0 ± 1.9 mL, P = .014) increased but LV end-systolic volume remained unchanged (58.2 ± 2.2 mL, P = .21) at 20 weeks compared with 8 weeks. Nevertheless, LVEF increased significantly at 20 weeks compared with 8 weeks (43.7 ± 2.8%, P = .006). The LVEF in the control group was significantly lower than the patch group at 20 weeks (P = .05). Furthermore, the percentage increase in LV end-diastolic volume (+14.1 ± 1.8% vs. +6.6 ± 2.1%, P = .015) and LV end-systolic volume (+12.1 ± 2.4% vs. −4.7 ± 3.7%, P = .0015) from 8 to 20 weeks were significantly greater in the control group compared with the patch group (Fig. 4D). On the other hand, the percentage increase in LVEF...
(+17.3 ± 4.9% vs. +4.1 ± 3.9%, P = .048) from 8 to 20 weeks was significantly greater in the patch group compared with the control group.

**Histology**

Gross examination showed lack of adhesion of the expanded polytetrafluoroethylene material on the pericardial side of the patch with the chest wall. Transverse cross-sections of the LV demonstrated that the polypropylene mesh on the epicardial side of the patch was well merged with the cardiac tissue and restored the LV wall thickness relative to those hearts from the control group (Fig. 5A). The average LV wall thickness at the infarct region and the adjacent peri-infarct regions in the transverse direction from both sides regions were measured from 5 random samples in each animal. Both the LV wall thickness at the infarct region (0.77 ± 0.07 mm vs. 0.53 ± 0.05 mm, P = .046) and adjacent peri-infarct regions on the left side (1.27 ± 0.08 mm vs. 0.81 ± 0.06 mm, P < .001) and on the right side (1.23 ± 0.05 mm vs. 0.84 ± 0.08 mm, P < .001) at transverse section were significant greater in the patch group compared with the control group (Fig. 5B).

Histological sections showed integration of the polypropylene mesh with the myocardium without evidence of inflammation, and the expanded polytetrafluoroethylene material remained intact (Fig. 6A). Furthermore, the infarcted LV walls of the patch group were thicker and contained more dense and muscle-like bundles than those of the control group (Fig. 6A). Immunohistochemistry study demonstrated significantly lower number of MMP-9 positive cells at the peri-infarct zone in the patch group compared with the control group (96.0 ± 12.1 cells/mm² vs. 248.7 ± 39.1 cells/mm², P = .008), suggesting attenuation of the ventricular remodeling process in the patch group (Fig. 6B).

**Discussion**

Previous studies have demonstrated the potential of using a passive (without contracting cardiomyocyte) or active (with contracting cardiomyocytes) epicardial patch to prevent LV adverse remodeling and to improve LV function during the early phase of MI.10,11,16 Furthermore, recent studies17,18 have also shown that injection of biopolymer into chronic infarct regions can prevent LV remodeling. In addition to regional LV reinforcement, these biopolymers can also influence local microenvironment to enhance angiogenesis.18 However, the impact of regional LV reinforcement with a passive epicardial patch alone during the late phase of MI, when LV remodeling has already commenced, remains unclear.
In this study, we evaluated the hypothesis that a passive epicardial patch can prevent the progression of pathological LV remodeling and thus improve LV contractile function. Serial cardiac MRI was used to evaluate the changes in LV dimension and function after patch implantation. Our results demonstrate that this patch, implanted over the infarcted LV region, in a large animal model of chronic MI with impaired LVEF, increases regional LV wall thickness, reduces adverse LV remodeling, and improves LV function compared with control animals. Although progressive LV dilation was still observed in the patch group, the degree of changes in LV dimension, especially the LV end-diastolic volume as measured by cardiac MRI, was significantly less than in the control group. Despite not directly contributing to improving LV contractile function, prevention of progressive LV dilation by the epicardial patch was associated with significant improvement in +dP/dt and LVEF. These beneficial effects were observed even though the patch was placed 8 weeks post-MI, in which the process of pathological LV remodeling with infarct expansion and LV wall thinning have been taken place.19 In this study, some degree of LV dilation have been observed at 8 weeks post-MI because of both infarct and non-infarct zone dilation. The placement of epicardial patch over the infarct zone would have limited the dilation in the infarct scar zone but the dilation of the noninfarct zone would be expected to progress. Indeed, progressive LV dilation was still observed after patch placement which might attribute to the dilation in the peri-infarct zone. Nevertheless, the expression of MMP-9, which has been shown to play an important role in post-MI LV remodeling,20,21 was decreased at the peri-infarct zones in the patch group as compared with control group. This finding suggests epicardial patch might also limit per-infarct zone dilation and remodeling.

A modified commercially available synthetic mesh, composed of 1 layer to minimize adhesion formation and another layer to promote tissue ingrowth, was used in this study. The monofilaments of polypropylene are biocompatible and provide sufficient mechanical strength for the mesh as used in the hernias repair.22 Furthermore, the large pore size polypropylene can reduce the inflammatory response as well as the weight of the mesh such that it is amenable to rolling or other compression methods for deployment via a minimally invasive procedure. After 12 weeks of implantation, the majority of the layer on the epicardial side of the patch showed good integration with the myocardium without evidence of inflammation, whereas the layer on the pericardial side had minimal

---

**Fig. 4.** (A) Left ventricular (LV) end-diastolic volume (LVEDV), (B) LV end-systolic volume (LVESV), (C) LV ejection fraction (LVEF), and (D) the percentage changes in LVEDV, LVESV, and LVEF measured by cardiac magnetic resonance imaging in control group and patch group at 8-week and 20-week assessment.
adhesion to the pericardium. In this study, biodegradable biomaterials as previously reported were not used, because we postulated that a permanent mechanical support might be necessary for attenuation of LV remodeling during the chronic phase. Furthermore, direct injection of biomaterial into infarct regions requires invasive open heart procedure, whereas implantation of a passive patch can be performed by minimally invasive procedure. In addition, we expected that the epicardial patch that we tested would provide regional LV reinforcement while avoiding pericardial adhesion and the associated LV restriction and impairment of coronary blood flow that have been reported for LV restraint devices. Indeed, invasive hemodynamic study showed no evidence of impairment of LV diastolic filling as reflected by $-\frac{dP}{dt}$ after patch implantation.

In contrast to previous experimental studies using an LV restraint device in which LV reverse remodeling was observed, our results demonstrated that regional LV reinforcement post-MI could only reduce the extent of LV adverse remodeling. Several possible mechanisms might account for the progressive LV remodeling after patch implantation. First, although the epicardial patch increased the LV wall thickness at the underlying infarct region, this region still evinced significant thinning compared with the adjacent peri-infarct region. Therefore, regional reinforcement may attenuate, but not completely eliminate, the increase in wall tension at the infarct. Second, the use of a fixed size epicardial patch should not be able to cover all the infarcted regions. Therefore, the extent and amount of regional ventricular restraint might need to be optimized to further reduce myocardial work load to enable LV reverse remodeling. Third, the use of a fixed size epicardial patch might not cover all the infarcted. Finally, the beneficial effect of the epicardial patch might be greater if administered earlier during the post-MI remodeling process; this requires further research. Nevertheless, the findings of this study have potential important clinical implications. Despite the advances in

---

**Fig. 5.** (A) Representative examples of transverse section of left ventricular (LV) at 20-week in control group and patch group. Black arrow points to the implanted patch, red arrows indicate the LV wall thickness of adjacent peri-infarct regions at left and right side in the transverse sections, and blue arrows indicate the LV wall thickness of the infarct regions. (B) Measurement of LV wall thickness at the infarct regions and peri-infarct regions in control group and patch group.
coronary revascularization therapies, a significant proportion of patients with acute MI still miss their opportunities to receive timely coronary reperfusion and develop post-MI heart failure from progressive LV remodeling. Furthermore, adverse LV remodeling is still observed in many patients treated with coronary reperfusion and optimal post-MI medical therapies. Progressive LV remodeling after MI is a major predictor of morbidity and mortality from heart failure and life-threatening arrhythmias. Therefore, regional LV reinforcement over the infarct region with the use of an epicardial patch may provide an alternative therapy to attenuate LV remodeling in those patients who fail medical therapies or coronary reperfusion post-MI. Furthermore, this type of epicardial patch can be potentially delivered by a minimally invasive procedure to avoid the complication of major cardiac surgery; it may also be combined with pacing or defibrillation electrodes for cardiac pacing or the prevention of sudden death.

**Study Limitations**

First, the beneficial effects on LV remodeling and function were only observed 12 weeks after patch implantation. The longer term functional effect as well as any structural changes to the patch should be investigated for longer periods of follow-up. Second, this approach may be infeasible or possibly contraindicated in those patients who have previously undergone, or may need in the future, open heart surgery, or in those with a history of pericardial diseases. Third, except for invasive measurement of $-dP/dt$, other diastolic index was not measured in the study. Fourth, detailed quantitative assessment of the changes in fibrosis and collagen content could not be performed as the patch also showed positive staining with Masson’s trichrome. Finally, the potential impact of other medical therapies, such as β-blocker and angiotensin-converting enzyme inhibitor, on the efficacy of the epicardial patch was not investigated in this study. Whether the patch can provide incremental benefit on top of these medical therapies remains unclear.

**Conclusions**

This report confirms findings in previous experimental studies and extends them to show that regional application of a simple, passive synthetic epicardial patch increases LV wall thickness at the infarct region, attenuates LV dilation, and improves LVEF in a large animal model of chronic MI.
These findings serve as proof of principle to support the development of this treatment approach as a therapeutic option in patients with progressive post-MI LV remodeling despite optimal medical therapy.

Disclosures

Michael E. Benser, Stuart P. Rosenberg, and Euljuon Park are employees of Cardiac Rhythm Management Division, St. Jude Medical, USA; Hung-Fat Tse and Chu-Pak Lau received honorarium and research grant from Cardiac Rhythm Management Division, St. Jude Medical, USA.

References