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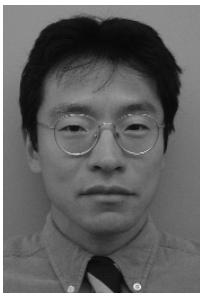
An Experimental Rabbit Model for Off-Pump Left Ventricular Reconstruction Following Left Ventricular Aneurysm



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ABSTRACT

Background. Cardiac electromechanical remodeling following left ventricular reconstruction (LVR) surgery is not fully understood. Further development of an animal model will facilitate investigations in this area. In the present study, we aimed to establish a novel LVR procedure without the use of cardiopulmonary bypass in a rabbit left ventricular (LV) aneurysm model.

Methods. LV aneurysm was created in 6 rabbits by ligation of the distal left coronary artery. More than a month later, LVR aneurysm surgery was performed off-pump using a purse-string suture around the aneurysm. Cardiac dimensions and function were evaluated using echocardiographic techniques perioperatively and 4 weeks after LVR surgery. Six structurally normal hearts were used as controls.

Results. LVR surgery was successfully performed in all 6 rabbits. Both LV end-diastolic volume (LVEDV, 4.6 ± 0.9 to 3.3 ± 0.6 mL; $P < .01$) and LV end-systolic volume (LVESV, 2.5 ± 0.6 to 1.5 ± 0.2 mL, $P < .01$) were decreased immediately postsurgery versus presurgery, and LV ejection fraction (LVEF) was increased (44.5 ± 5.3 to 55.6 ± 4.8%, $P < .001$). For comparison, in normal rabbits (n = 6), LVEDV, LVESV and LVEF were 3.1 ± 0.7 mL, 1.2 ± 0.5 mL, and 64.5 ± 8.8%, respectively. During follow-up, one rabbit died 3 weeks after surgery from an unknown cause. In the remaining 5 animals, improvements of LVEDV (3.7 ± 0.4 mL, $P < .05$), LVESV (1.7 ± 0. 3 mL, $P < .01$), and LVEF (53.1 ± 2.8%, $P < .01$) were maintained versus presurgery values for more than 4 weeks after LVR.

Conclusions. Off-pump LVR of rabbit LV aneurysm is an effective and less invasive surgery that resulted in sustained improvement in cardiac function with no gross intraoperative or postoperative mortality. This may be a useful model for investigations of electromechanical remodeling following LVR.

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INTRODUCTION

Left ventricular aneurysm is associated with progressive remodeling of the left ventricle (LV) characterized by LV dilatation and deformation of chamber shape leading to impaired pump function. As a result, patients may experience heart failure symptoms. Clinical LV aneurysm repair seeks to exclude the infarct scar in an effort to normalize LV volume and cardiac geometry, attenuate elevated wall stresses, and restore cardiac function. LV aneurysm repair has also been evaluated in animal models. Most of these studies have focused on optimizing hemodynamic performance and such surgery has improved cardiac pump function in the short to medium term. However, the long-term effects of surgery on ventricular remodeling and on cardiac function are less well characterized. Furthermore, the impact of such surgical interventions on cardiac electrical remodeling is largely unexplored. Because the surgeries are performed on patients at increased risk of sudden death due to lethal cardiac arrhythmias, it is important to understand both the effects of surgery and the subsequent remodeling on cardiac electrical properties and the mechanisms of arrhythmogenesis. It is neither feasible nor ethical to perform a prospective study of these phenomena in patients. Animal research provides such an opportunity. LV aneurysm repair research has mostly been conducted in a large animal model (sheep) [Savage 1992; Ratcliffe 2000] and in a small animal model (rat) [Schwarz 2000; Nishina 2001; Kanashiro 2002; Matsubayashi 2003]. Although large animal models are suitable for physiological investigations, they are expensive and time consuming for the chronic studies necessary for cardiac electrophysiology investigations or for long-term studies of LV function. Small animal models are favored because of their time- and cost-saving nature. However, action potential morphology and other electrophysiologic features of the rat heart do not closely resemble those of human hearts. Cardiac electrophysiology of the rabbit heart more closely resembles that of the human heart. Furthermore, the rabbit is a better model for in vitro research on the mechanisms of arrhythmogenesis. This is due to its ability to sustain clinically relevant

arrhythmias, not typically observed in smaller species such as the rat and mouse. The time course and the extent of the development of coronary collaterals in the rabbit in response to myocardial infarction (MI) are also similar to humans [Maxwell 1987].

The purpose of this study was to develop a new, less-invasive rabbit LV reconstruction (LVR) model for treatment of LV aneurysms without employing cardiopulmonary bypass. Successful establishment of this model would be characterized by low intraoperative or postoperative morbidity and mortality and by sustained improvement of cardiac function. A new model of LV aneurysm plication in the rabbit may offer a research bridge between large and small animal models. This model may provide a useful tool for long-term studies because of its relatively low cost and may also be a useful model for studying cardiac electrophysiologic changes in a surgically repaired heart.

MATERIALS AND METHODS

Thirteen New Zealand white rabbits, bred at Oakwood Research Facility (Oxford, MI, USA) and purchased from Harlan (Indianapolis, IN, USA), were used in this study. This study was approved by the Cleveland Clinic's Institutional Animal Care and Use Committee, and all animals received humane care in accordance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press (revised 1996).

In Vivo First Survival Surgery: Creation of an LV Aneurysm

Seven rabbits (either sex, 3.1 ± 0.4 kg; range, 2.6-3.5 kg) received surgeries, and 6 rabbits (3.1 ± 0.3 kg; range, 2.8-3.6 kg) were used as a control. Rabbits were first anesthetized intramuscularly with ketamine (35 mg/kg) and xylazine (5 mg/kg). A 22-gauge intravenous catheter was inserted into the marginal ear vein for continuous infusion of normal saline solution during the surgery. Rabbits were then intubated with an endotracheal tube (3.0-mm internal diameter) and mechanically ventilated (rate, 76 breaths/min; tidal volume, 8 mL) with a mixture of isoflurane (1.0%-2.0%) and oxygen. The rabbits were placed on a water blanket maintained at 38°C, and the electrocardiogram (ECG) was monitored continuously.

The chest was opened through the fourth left intercostal space, and the heart was exposed via incision of pericardium. An LV aneurysm was created by ligating the lateral division of the left coronary artery (LCA) in hearts with trifurcated epicardial LCA distribution patterns (n = 3) at a level of 60% to 70% from the apex (Figure 1) as previously reported by other investigators [Podesser 1997; Lee 2002]. In the remaining rabbits with a bifurcated distribution pattern of the LCA, the posterolateral division was ligated at a level of 40% to 50% from the apex (n = 3). Immediately before ligation, lidocaine (1 mg/kg) was intravenously administered to minimize potential ventricular arrhythmias. Both transesophageal (TEE) and epicardial (EE) echocardiography (10.0 MHz AccuNav transducer; Siemens, New York, NY, USA) recordings were used during the surgery. EE was useful for assessing the extent of the infarcted area and LV wall motion abnormality caused by ligation of the coronary artery, as we could directly place an echo-probe on the infarcted area for optimal resolution. The TEE provided better detection of mitral regurgitation (MR) as well as the possibility of reproducing the same echo views as those taken during the follow-up studies. LV end-diastolic volume (LVEDV), end-systolic volume (LVESV), and ejection fraction (LVEF) were measured by Simpson's method. MR was assessed by TEE using a 5-point scale (0 = none; 1 = mild; 2 = moderate; 3 = moderate-severe; 4 = severe). Successful ligation was also confirmed by visual inspection for the presence of myocardial cyanosis with bulging of the ventricular wall and ST-segment elevation in the ECG signal (Figure 1).

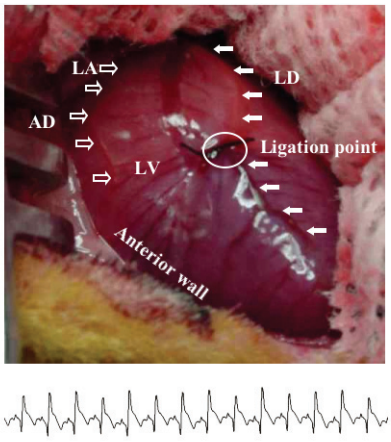

Figure 1. A typical location of the left coronary artery ligation in a heart with trifurcated distribution of the left coronary artery during surgery to create the left ventricular aneurysm. An anterior-lateral view of the heart is shown. A ligature was placed at the lateral division of the left coronary artery approximately 65% from the apex between the atrioventricular groove and apex. The posterior division is not visible in this picture. An electrocardiogram trace after the artery ligation is shown at the bottom. LA indicates left atrium; LV, left ventricle; AD, anterior division; LD, lateral division.

Following ligation, a chest tube was inserted into the thoracic cavity and the lungs were inflated. The ribs on both sides of the surgical incision were approximated by 3 evenly placed loops of heavy-duty thread, and the thoracic cavity was sealed via multiple suture layers. The chest tube was withdrawn while negative pressure was applied. A long-lasting antibiotic was administered prior to the surgery, and an analgesic was provided postoperatively for 3 days. Morphological and histological changes were examined in 1 additional rabbit at 1 week following MI surgery.

In Vivo Second Survival Surgery: Plication of an LV Aneurysm

After more than 4 weeks of recovery (43.5 ± 25.3 days), a transthoracic echocardiography (TTE) (6.0 MHz transducer, Vivid 7; GE Medical, Piscataway, NJ, USA) was performed to ascertain the presence of LV aneurysm. Anesthesia was induced and maintained according to the protocol of the initial surgery. The heart was exposed via a left thoracotomy

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through the fifth intercostal space, and a 3-0 polypropylene suture was passed through the viable heart muscle around the infarcted area in a circular fashion. A strip of polytetrafluoroethylene felt was used for reinforcement (Figure 2A). Under TEE and EE guidance, 2 horizontal 3-0 prolene sutures were placed close to the residual cavity of the LV plication (Figure 2B). Photos of a heart with LV aneurysm in the pre-LVR and post-LVR state are shown in Figures 2C and 2D, respectively.

TTE was repeated 4 to 6 weeks after the LVR procedure. The infarct perimeter was defined as the length of the LV endocardium with wall motion abnormality in end-diastole from the apical 4-chamber view, and the infarct percentage was expressed as the ratio of the infarct perimeter to the total LV perimeter in end-diastole [Popovic 1996]. The same echocardiographic protocol was completed in the 6 control rabbits without MI to compare the measurements between normal rabbits and those with LV aneurysm.

Statistical Analysis

Data were expressed as mean ± standard deviation. An unpaired *t* test was used to test the significance between normal rabbits and rabbits with LV aneurysm. A one-way analysis of variance was used to evaluate the echocardiographic data, and a Fisher's least significant difference test was performed as a post hoc comparison. *P* values < .05 were considered statistically significant.

RESULTS

Rabbits with LV aneurysm (n = 6) developed dilated LV chambers and had reduced LVEF compared to that of normal control rabbits (n = 6) (LVEDV, 4.6 ± 0.9 versus 3.1 ± 0.7 mL, $P < .01$; LVESV, 2.5 ± 0.6 versus 1.2 ± 0.5 mL, $P < .01$; LVEF, 44.5 ± 5.3 versus 64.5 ± 8.8%, $P < .01$, respectively). In 3 rabbits with LV aneurysm, preinfarction echo measurements were available. In these 3 cases, progressive LV dilatation occurred almost linearly during the 4 weeks after infarction (Table 1).

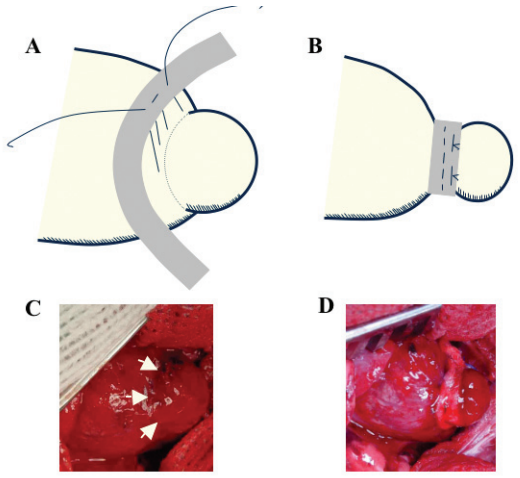

Figure 2. Technique for left ventricular reconstruction (LVR) without cardiopulmonary bypass. A, A 3-0 polypropylene suture was passed through the muscular edge of viable muscle in a circular fashion and a strip of polytetrafluoroethylene felt was used for reinforcement. B, Two horizontal 3-0 prolene sutures were placed close to the residual cavity of the left ventricular aneurysm. C, Photo of a heart with a left ventricular aneurysm just prior to LVR. The arrows identify the neck of the left ventricular aneurysm. D, Photo of the same heart just after LVR.

Table 1. Progression of Left Ventricular Enlargement and Infarct Area (n = 3)*

	Baseline	Just after MI	1 Week after MI	4 Weeks after MI
LVEDV, mL	3.3 ± 0.5	3.4 ± 0.4	3.7 ± 0.3	4.6 ± 0.7
LVESV, mL	1.1 ± 0.1	2.1 ± 0.1	2.2 ± 0.2	2.6 ± 0.1
LVEF, %	66 ± 5	39 ± 6	41 ± 1	42 ± 8
Infarct perimeter, mm	0	2.4 ± 0.3	2.6 ± 0.1	3.1 ± 0.4
Infarct percentage, %	0	41 ± 4	45 ± 5	48 ± 6

*MI indicates myocardial infarction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

LVR was successfully performed in all 6 cases with LV aneurysm. Results of the echocardiographic measurements are summarized in Table 2. Immediately after the LVR surgery, the LVEDV and LVESV were both significantly decreased (Figure 3), while LVEF was significantly increased. In addition, the infarct perimeter and infarct percentage were also reduced immediately after the procedure. All animals were extubated within 1 hour after the surgery and recovered well during the postoperative period without any complications. However, 1 rabbit died 3 weeks after the LVR surgery from an unknown cause. In the remaining 5 animals, improvements of LVEDV, LVESV, and LVEF along with reduction of infarct perimeter and infarct percentage were maintained for more than 4 weeks after undergoing LVR surgery (Table 2).

Table 2. Echocardiographic Measurements before and after LVR*

	Before LVR	Just after LVR	More than 4 Weeks after LVR
Number of rabbits	6	6	5
LVEDV, mL	4.6 ± 0.9	3.3 ± 0.6†	3.7 ± 0.4‡
LVESV, mL	2.5 ± 0.6	1.5 ± 0.2†	1.7 ± 0.3†
LVEF, %	44.5 ± 5.3	55.6 ± 4.8†	53.1 ± 2.8†
Infarct perimeter, mm	3.1 ± 0.3	1.9 ± 0.4†	1.8 ± 0.1†
Infarct percentage, %	50.0 ± 6.2	35.8 ± 6.8†	33.8 ± 4.9†
MR ≥ 2+	1/6	2/6	0/5

*LVR indicates left ventricular reconstruction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

†$P < .01$ versus before LVR.

‡$P < .05$ versus before LVR.

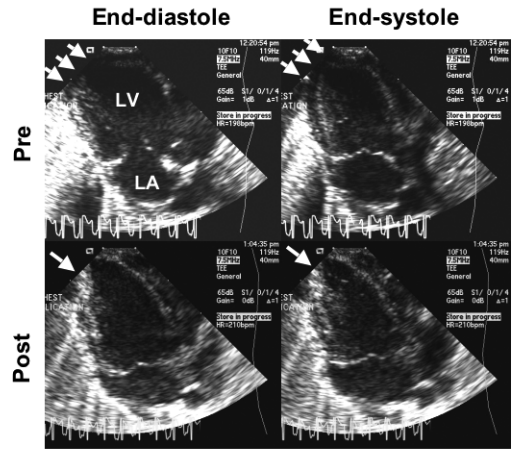

Figure 3. Echocardiograms before and after the left ventricular reconstruction (LVR) procedure. Multiple arrows in the pre-plication indicate the infarcted region. The single arrow in post-plication corresponds to the plicated hyperechogenic region. LA indicates left atrium; LV, left ventricle; Pre, pre-LVR or pre-plication; Post, post-LVR or post-plication.

To further confirm the existence of an LV aneurysm and to verify how plication surgery was completed, autopsies were performed on a representative heart after MI and a heart following plication (Figures 4 and 5, respectively). Figure 4A shows a photo of a 1-week-old MI heart that was Langendorff-perfused. Gross examination of the heart revealed a protruding LV aneurysm. Microscopic examination of a hematoxylin- and eosin-stained cross section from the infarct region revealed a large, transmural infarction in the LV (Figure 4B). Seven weeks after reconstruction surgery, LV volume was reduced and geometry was restored closer to normal. There was no thrombus or residual cavity around the plicated area (Figure 5). All of these observations are consistent with our echocardiographic findings.

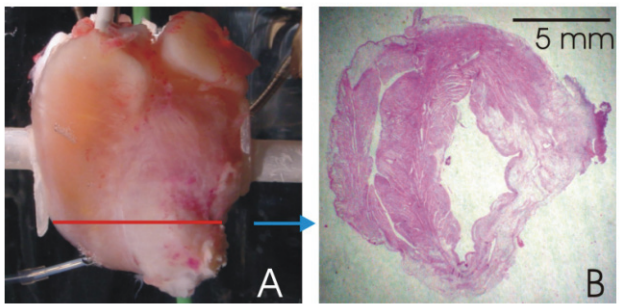

Figure 4. Development of a left ventricular aneurysm in a heart with a 1-week-old myocardial infarction. A, Photograph of the heart. The red line indicates the location of tissue obtained for analysis in Figure 4B. B, Histological cross section of the heart stained with hematoxylin and eosin.

DISCUSSION

This study demonstrated that (1) rabbit models with an LV aneurysm were easily and safely created, (2) LVR was successfully performed in all rabbits with minimal complications, and (3) LV function was improved immediately and the improvement was sustained for more than 4 weeks after the off-pump LVR procedure.

Several clinical LVR studies have been reported since 1985 [Jatene 1985; Kesler 1992; Shapira 1997; Dor 1998; Lundblad 2003; Buckberg 2004; Schenk 2004]. More recently, techniques for clinical off-pump LVR in patients have also been reported by other investigators [Furutachi 2005; Hendzel 2005; Yu 2005]. In animal research, Markovitz and associates reported a large animal model of LV aneurysm using a sheep [Markovitz 1989]. Walker and associates also performed an LVR in a sheep model of LV aneurysm, but the procedure required cardiopulmonary bypass [Walker 2005]. Komeda and associates reported animal models of LVR in rats [Nishina 2001; Sakaguchi 2001; Sakakibara 2002]; however, only horizontal mattress sutures were used for the plication and thus these techniques did not represent "true" LVR but rather only linear repair. Komeda and his colleagues [Nishina 2001] also reported that the initial improvement of the linear repair was not sustained for 4 weeks in the rat ischemic cardiomyopathy model. In their model, 4 weeks after surgery, cardiac function had returned to the levels similar to the status before the LVR surgery. In our study, although the LVEDV, LVESV, and LVEF were not fully restored to the baseline values of normal rabbits immediately after the LVR, significant improvements in LVEDV, LVESV, and LVEF were achieved via surgery. Moreover, these improvements persisted for more than 4 weeks after the LVR procedure.

Several studies were also conducted to investigate the superiority of LVR to simple linear plication with regard to early and late clinical outcomes [Kesler 1992; Shapira 1997; Lundblad 2003; Buckberg 2004]. However, the linear repair technique may have limitations as a chronic experimental model when compared to the novel technique we report here, which is more similar to the circular plication used in clinical cases [Schenk 2004]. To definitively address this, in the future we will need to study a linear plication-only group to com-

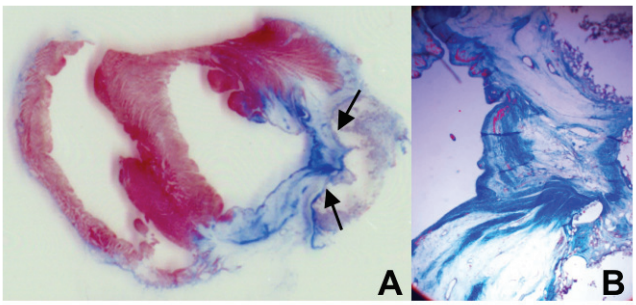

Figure 5. Histological cross section (Masson's trichrome staining) from a heart 7 weeks after left ventricle plication. A, The arrows indicate the plicated region. B, A close-up histology of plicated region.

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pare the linear-plication approach with our novel approach in this animal model.

A potential risk associated with the use of our technique is dislodgement of a thrombus attached to the LV wall. Although pre- and postoperative echocardiographic studies revealed no thrombus formation within the LV cavity in this study, one animal died due to an unknown cause. Further studies with longer follow-up periods will be needed.

Aside from the novel plication technique we used, we believe that the combined use of TEE and EE intraoperatively during both surgeries also helped to assure the success of the surgeries. Furthermore, this animal model requires 2 operations (one for inducing aneurysm and the other for repairing the LV), which is more demanding than just 1 operation because the second operation is often associated with increased bleeding due to adhesion between the heart and the surrounding tissue. Moreover, the LV was repaired without cardiopulmonary bypass and with the heart beating. We overcame these difficulties by (1) employing different approaches to the heart (ie, left thoracotomy at the fourth intercostal space for the first surgery, and at the fifth intercostal space for the second surgery); (2) making the thoracotomy large and dissecting the heart carefully under magnifying glasses during the second operation, using electrical cautery as required; (3) minimizing the displacement of the heart to reduce bleeding and avoid tearing the LV tissue during plication of the LV; and (4) most importantly, the operations were performed by fully trained surgeons. With these efforts, no rabbits died during or immediately after the LVR surgeries.

Although the time course and extent of the development of coronary collaterals in rabbits following MI are similar to that in humans [Maxwell 1987], it is notable that variability of coronary artery distribution in rabbits differs from that in humans. In rabbits, the left anterior descending artery (LAD) is not a dominant artery. Thus ligation of the branches of the LAD is not performed to create infarctions in the rabbit model. A uniform classification of epicardial branching of the coronary arteries in rabbit hearts has been proposed by Podesser and associates [Podesser 1997]. The study revealed 2 patterns of LCA distribution: a bifurcation pattern (in half of the animals investigated) and a trifurcation pattern. The bifurcation pattern has 2 branches of the LCA, the anterior and posterolateral divisions, whereas the trifurcation pattern has a constant dominant lateral division in addition to the anterior and posterior divisions. Creation of a chronic rabbit heart failure model based on this new concept of bifurcation/trifurcation classification has also been reported [Lee 2002]. In our study, we observed a similar bifurcation/trifurcation (3/3) branching pattern in the 6 rabbits studied. Our ligature location (see Methods section) is close to that reported by Lee and associates [Lee 2002]. Note that in this rabbit model we created the infarcts, which were mainly located in the LV anterior-apical region, as shown in Figures 1 and 2. The lateral wall is less infarcted than the anterior wall. It should also be emphasized that the rabbit heart has minimal coronary collateral arteries and lacks a transmural gradient of the collateral blood flow, all analogous to a normal human heart [Maxwell 1987]. As a result, MI is frequently transmural. In a study published recently by our group, 8/8 myocardial infarcted rabbit hearts had transmural infarcts [Li 2005].

Study Limitations

In this study, LV aneurysm plication was performed 4 weeks following first surgery despite the fact that at 4 weeks postinfarction dilation of LV and deterioration of LV function had not been fully stabilized. There was also a slight redilation of the LV more than 4 weeks after LVR compared to the status immediately after the surgery. In both cases, further study with a longer follow-up period will be needed to address whether or when dilation of LV and deterioration of LV function reaches a plateau, or whether the trend of LV redilation continues over time following LVR in this model. Another limitation of this study is that we did not study a linear-plication–only group. Thus we could not compare our novel approach to the linear-plication approach directly in our model. Further studies are needed to clarify this issue.

SUMMARY AND CONCLUSION

Off-pump LV plication in the rabbit is an effective, semi-invasive technique that did not result in gross intraoperative or postoperative mortality. It was characterized by a significant decrease in LV volumes, improved cardiac function, and the improvement in ventricular geometry and function was sustained for more than 4 weeks. The rabbit model of LV aneurysm plication offers a bridge for research between the large animal (sheep) and small animal (rat) LVR models and may be a more affordable and useful model for studying long-term cardiac function and cardiac electrophysiological changes following surgical interventions. Thus, this model may facilitate further investigations in areas relating to LV remodeling and its treatment (including LVR), not only from a hemodynamic perspective but also from an electrophysiologic one.

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