Ventricular Constraint Using the Acorn Cardiac Support Device Reduces Myocardial Akinetic Area in an Ovine Model of Acute Infarction

James J. Pilla, PhD; Aaron S. Blom, BA; Daniel J. Brockman, BVSc; Frank Bowen, MD; Qing Yuan, PhD; Joseph Giammarco, PhD; Victor A. Ferrari, MD; Joseph H. Gorman, III, MD; Robert C. Gorman, MD; Michael A. Acker, MD

Background—Left ventricular remodeling secondary to acute myocardial infarction (AMI) is characterized by ventricular dilatation and regional akinesis. In this study, we investigated the effect of passive constraint on akinetic area development.

Methods and Results—The effect of passive constraint on akinetic area was investigated in 10 sheep using tissue-tagging magnetic resonance imaging (MRI). A baseline MRI study was followed by the creation of an anterior infarct. After 1 week, the animals received a second MRI study. A cardiac support device (CSD) was then placed over the epicardium in 5 sheep whereas the remaining animals served as controls. A terminal study was performed at the 2-month postinfarct in both groups. The akinetic area at 1-week postinfarct was similar in both groups. At the terminal time-point, the akinetic area in the control group was similar to the 1-week time-point whereas in the CSD group, the area of akinesis decreased (P < 0.001). A comparison of the 2 groups at the terminal time-point demonstrates a significantly diminished area of akinesis in the CSD group (P < 0.004). The relative area of akinesis followed a similar pattern. End-systolic and end-diastolic wall thickness was significantly greater in the CSD group at terminal (P < 0.001). In addition, the minimum wall thickness was greater in the CSD group compared with the controls (P < 0.04).

Conclusions—Passive constraint reduced akinetic area development secondary to AMI. The attenuation of regional wall stress may prevent the incorporation of the border zone into the infarct, decreasing infarct size and providing a promising new therapy for patients after an AMI. (Circulation. 2002;106[suppl I]:I-207-I-211.)

Key Words: ventricles • remodeling • myocardial infarction • magnetic resonance imaging

Acute myocardial infarction can be a stimulus for left ventricular remodeling, which is characterized by dilatation and global and regional functional impairment with an increased risk of heart failure.1–5 Although the left ventricle undergoes significant architectural and functional changes, such as loss of functional cardiac units, myocyte hypertrophy, and interstitial cellular fibrosis6 because of myocardial loss by infarction, the mechanisms underlying this remodeling process are not completely understood. Additionally, the degree of left ventricular enlargement has been identified as being associated with an unfavorable clinical outcome.7

The increase in ventricular volume after myocardial infarction (MI) is fueled by an increase in wall stress, which increases the workload of the left ventricle. Subsequently, the heart enters into a positive feedback loop of dilatation and further exaggeration of wall stress, which leads, ultimately, to progressive global and regional dysfunction and end-stage heart failure. Studies using pharmacological therapy such as β-blockers and angiotensin-converting enzyme inhibitors to reduce the loading conditions of the heart post-MI have demonstrated a significant improvement in cardiovascular mortality by curbing the detrimental effects of ventricular remodeling.8–10 Until recently, medical therapy, as described above, was the mainstay of treatments for patients suffering from the debilitating effects of heart failure. However, the latest advancements in the surgical treatment of heart failure have shown promise in improving cardiac function and promoting reverse remodeling in these patients. Additionally, recent studies using a mesh patch placed directly over the infarct itself have been shown to preserve ventricular geometry and function.11

The loss of myocytes after an MI leads to the thinning and elongation of the infarct region and has been described as infarct expansion.12 Expansion of the infarct occurs early after the event, resulting in an increase in wall stress that promotes the global process of ventricular dilatation. Subsequent ventricular remodeling as well as heart failure and death can be correlated to the extent of infarct expansion.13

From the Departments of Surgery (J.J.P., D.J.B., F.B., J.H.G., R.C.G., M.A.A.), Radiology (A.S.B., Q.Y., J.G.), and Medicine (V.A.F.), University of Pennsylvania Medical Center, Philadelphia, Pa. Correspondence to Michael A. Acker, MD, Associate Professor of Surgery, Hospital of the University of Pennsylvania, 6th Floor Silverstein Pavilion, Philadelphia, PA 19104.
© 2002 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.cir.0000032871.55215.de

I-207
In this study, we investigated an alternative method of reducing wall stress by mechanically limiting progressive myocardial dilatation after an infarct using a bidirectional woven polyester jacket (Acorn Cardiac Support Device [CSD], Acorn Cardiovascular, Inc, St. Paul, MN) with the hypothesis that placement of the CSD postinfarction leads to a decrease in border zone involvement and a decreasing akinetic/thinned area surrounding the ischemic area. Magnetic resonance imaging (MRI) with tissue tagging was used to investigate the effects of passive ventricular constraint in an ovine model of acute MI.

Materials and Methods
All animals used in this study received care in compliance with the “Guide for Care and Use of Laboratory Animals” published by the National Institutes of Health (NIH publication 86 to 23, revised 1985), and the investigation was approved by the Institutional Animal Care and Use Committee.

Study Design
The effect of passive constraint on akinetic area was investigated in 10 Dorset sheep by using MRI with SPAtial Modulation of Magnetization (SPAMM)\(^{14}\) tissue tagging. The experimental protocol for this study consisted of performing a baseline MRI study followed by the creation of a transmural anterior wall MI, which was accomplished via a left thoracotomy and ligating the coronary arteries supplying the anterior wall. After a 1-week recovery period, the animals received a second MRI study and were then randomized to 1 of 2 groups, CSD retention or control. The custom polyester CSD was then placed over the ventricular epicardium in 5 sheep via the same thoracotomy used for infarct creation. All animals received no further medical or surgical intervention for the duration of the study. Additional tissue-tagged MRI studies were performed at the 2-month postinfarct time point in both the control and CSD groups.

Anesthesia
One hour before surgery, the animals were premedicated with 1 mg/kg acepromazine and 0.001 mg/kg glycopyrrolate. General anesthesia was induced with ketamine (10 mg/kg) and diazepam (0.5 mg/kg). Endotracheal intubation was performed, and the anesthesia was maintained with a mixture of isoflurane 1% to 2% in oxygen delivered by a time-cycled ventilator with a tidal volume of 20 mL/kg. Anesthesia was continuously adjusted and monitored to maintain a constant physiological state in the animals. General anesthesia was used for all the surgical procedures and for the duration of the MRI studies.

Animal Model
The anterior infarct model used in this study was originally characterized by Dr. L.H. Edmunds and his group at the University of Pennsylvania. This infarct model was chosen because it results in a significant increase in end-diastolic volume with a concomitant deterioration of function at 8 weeks postinfarct without the development of an apical aneurysm as seen with ligation of the left anterior descending.\(^{15}\) Moreover, mitral valve regurgitation is not created in this model at 8 weeks.\(^{15}\)

The infarct was created by exposing the heart via a left thoracotomy through the fifth interspace with a partial fifth rib resection. On opening the pericardium, the coronary anatomy was inspected to determine the vessels that were to be ligated. The criterion for ligation was any diagonal and/or obtuse margin vessel that supplied the anterior portion of the myocardium, excluding the left anterior descending. Before ligation, the animals were prophylaxed with a bolus of lidocaine and started on infusions of lidocaine and epinephrine. Systolic blood pressure was maintained at 80 mm Hg throughout the procedure using successive boluses of phenylephrine. The vessels were then ligated with 3-0 prolene. The chest remained open for an additional 45 minutes while the animal’s vital signs and ECG were continuously monitored to ensure the animal was stable. After this period, the pericardium in the 5 animals randomized to the CSD group was closed to minimize adhesions to the myocardium whereas the pericardium in the remaining animals was left open. The incision was closed in layers, and a chest tube was placed to drain the chest and evacuate the pneumothorax (the chest tube was removed once the animal became ambulatory). The animal’s vital signs and ECG were closely monitored for the initial 24-hour postoperative period before being sent back to the colony.

CSD Placement
One week post-infarct, the CSD was placed on 5 animals. The device is manufactured from a custom-designed bidirectional polyester weave that posses the material properties of being more compliant in the longitudinal direction then in the circumferential thus limiting circumferential dilatation but allowing longitudinal lengthening. The original thoracotomy was reopened and extended dorsally to allow resection of the remainder of the fifth rib. The pericardium was reopened to allow placement of the CSD, which was accomplished by sliding the device over the epicardium, up to the level of the atrioventricular junction. Prolene sutures (4–0) were placed along the base of heart starting on the posterior surface and working around anteriorly, with total of between 8 and 10 sutures depending on the size of the heart. The excess material was gathered up along a line parallel with the long axis of the heart. The thoracotomy was closed as before, and a chest tube was placed to evacuate the pneumothorax (and again removed when the

Figure 1. Representative diagram showing placement of the CSD over the ventricular epicardium. The CSD is secured at the base of the heart with interrupted sutures and sized to fit the circumference of the heart with a continuous suture in-line with the long axis of the heart.
animal became ambulatory. The animals received the same postoperative recovery measures as they did after the creation of the infarct.

MRI
At baseline, 1 week, and 2 months postinfarct, all animals underwent imaging in a 1.5T whole body high-speed clinical MR system (GE Medical Systems, Milwaukee, WI). Before imaging, the animals were placed under general anesthesia (as described above) and a left ventricular Millar catheter was inserted by means of a carotid artery cut-down. All images were cardiac and respiratory gated to ensure consistent spatial positioning of the heart during each acquisition. Tissue-tagged images in the short axis plane were acquired for this study.

Noninvasive tagging of cardiac tissue in MRI can be achieved by perturbing the local magnetization using SPAMM to create MRI-visible tags within the heart wall. As these tags move with the underlying heart wall, the motion of the tags during the cardiac cycle reveals the internal motion of the otherwise featureless heart wall resulting in a measure of regional strain.

The imaging parameters were as follows: field of view, 22 cm; TR/TE, 8.8/2.2 ms; slice thickness, 6 mm; interslice gap, 0; tag spacing, 5 mm; 2 signal averages; and 6 to 8 k-space lines acquired per cardiac frame (depending on heart rate). Images were acquired in the short axis plane using 2 surface coils (12.7 cm each) placed on the left and right chest. The images were archived and stored for offline analysis.

Data Analysis
An experienced observer in a blinded fashion performed all MRI image analysis. The short axis-tagged images were analyzed using a custom cardiac MRI analysis program, SPAMMVU.16 Left ventricular endocardial and epicardial contours were automatically delineated, and tag tracking was performed using an automated algorithm based on recently declassified military software adapted for cardiac MRI analysis.17 The akinetic area was measured as the portion of myocardium in the infarct zone that exhibited no strain change at end-systole or had thinned sufficiently enough to result in no visible tags. The area of akinesis was then determined by projecting 2 lines from the borders of the infarct to the centroid of the short axis plane. The angle of the intersection of these 2 lines was used to calculate the arc of the akinetic area. Knowing the length of this arc and multiplying by the slice thickness provided a precise measure of the area of akinesis. This procedure was performed for the entire short axis set of images and the measurements from each plane were summed to produce absolute akinesis area. Relative akinesis area was calculated by normalizing the absolute akinetic area by the end-systolic epicardial surface area.

Average end-systolic and end-diastolic wall thickness values were determined from the MRI. In the CSD group, wall-thickness measurements were the sum of myocardial wall thickness and CSD thickness because the MRI pulse sequence used could not differentiate between the two. Wall thickness was determined by fitting the end-diastolic and end-systolic endocardial and epicardial contours to a circle and calculating the difference between the radii of the 2 circles. Minimum wall thickness was ascertained by measuring the length of a line perpendicular to the epicardial and endocardial contours in the infarct zone.

Quantitative results were analyzed using a t test to determine significance between time points and groups.

Results
Nineteen sheep initially were enrolled in the study. Eleven of the animals completed the study, of which 6 were controls. Fifty-five percent of the animals that failed to complete the study died within 24 hours postinfarct, and 1 animal died after the baseline study before infarction. After randomization, 1 sheep in each of the 2 groups did not complete the study. The CSD sheep expired during the 2-month pressure-volume analysis (PVA) study because of undetermined causes whereas the control animal died before the 2-month time-point because of a bowel obstruction. A control animal was not included in the final statistical analysis because there was no left ventricular dilatation at 2 months postinfarct.

Representative SPAMM-tagged images of the left ventricle at mid-systole are shown in Figure 2. These images from the 2-month postinfarct study show both control and CSD animals. Note the diminished area of akinesis, as well as the increased wall thickness, in the CSD versus the control animal.

The measured akinetic area (Figure 3) at 1-week postinfarct was similar in both groups (P=NS). At the terminal time-point, the akinetic area in the control group was similar to the 1-week time-point (P=NS) whereas in the CSD group, the area of akinesis decreased (P=0.001). A comparison of the 2 groups at the terminal time-point demonstrates a significantly diminished area of akinesis in the CSD group (P=0.004).

The relative area of akinesis (Figure 4) followed a similar pattern as that of the absolute area. At 1-week postinfarct, the values for both groups were comparable (P=NS). The relative area of the control group at the terminal time-point remained similar to the 1-week point (P=NS) whereas in the CSD group, the relative area of akinesis decreased (P=0.001). A comparison of the 2 groups at the terminal time point demonstrates a significantly diminished relative akinetic area in the CSD group (P=0.013).

Measurements of myocardial wall thickness demonstrate that the CSD group experienced a reduced amount of wall thinning compared with the controls. End-systolic wall thickness measured at the terminal time point was significantly greater in the CSD group compared with the controls (P=0.001; Table 1). End-diastolic wall thickness demonstrated similar results with the CSD group having a thicker myocardium (P=0.001; Table
1). In addition, the minimum wall thickness was greater in the CSD group compared with the controls (control: 0.277±0.26 versus CSD: 0.50±0.34; P=0.04).

Discussion
The results of this study indicate that ventricular constraint using the Acorn CSD attenuates infarct development in an ovine model of acute MI. This is predicated on the assumption that an infarct is defined by thinned and/or akinetic myocardium. In addition, this device diminished end-systolic and end-diastolic myocardial wall thinning, which for the CSD group is the sum of myocardial wall thickness and CSD thickness.

An interesting finding is that the akinetic area and relative akinetic area for the controls did not change from 1 week to terminal whereas in the CSD group, the akinetic area, which was similar to controls at 1-week postinfarct, decreased over the same period. In addition, the results for the control group are consistent with the findings of Gorman et al15 using the identical ovine model of acute MI. They reported a relative infarct size measured by echocardiogram and postmortem examination at 8 weeks of 23.9%, which is consistent with the measurement we obtained by MRI at the same time point (25%±3%).

The similar akinetic area seen in both groups at 1-week postinfarct could be due to myocardial stunning in the border zone, which is frequently observed early after MI. This stunning in the border myocardium immediately after coronary occlusion has been attributed to differences in local wall stress distribution on the basis of mathematical models of the acutely infarcted left ventricle.18

![Figure 3. Bar graph indicating the measured area of akinesis at 1 week and 2 months postinfarct for both groups. The measured area of dysfunction at 1 week postinfarct was similar in both groups (P=NS). At the terminal time-point, the dysfunctional area in the control group was similar to the 1-week time-point (P=NS) whereas in the CSD group, the area of dysfunction decreased (P=0.001; t test). A comparison of the 2 groups at the terminal time point, however, demonstrates a significantly diminished area of dysfunction in the CSD group (P=0.004; t test).]

![Figure 4. Bar graph indicating the relative area of akinesia between the control and CSD groups. At 1 week postinfarct, the values for both groups were comparable (P=NS). The relative area of the control group at the terminal time-point remains similar to the 1-week point (P=NS), whereas in the CSD group, the relative area of dysfunction decreases (P=0.001; t test). A comparison of the 2 groups at the terminal time point demonstrates a significantly diminished relative area of dysfunction in the CSD group (P=0.013; t test).]
creased regional wall stress is due to the reduced end-systolic wall thickness\textsuperscript{19} and increased ventricular radius. If left untreated, the increased regional wall stresses favors permanent dysfunction of the border zone and progressive wall thinning.\textsuperscript{20} This results in the adjacent akinetic myocardium being pulled into the infarct.

It is hypothesized that placement of the CSD inhibits migration of the akinetic border zone into the infarct by decreasing regional myocardial wall stress. This is accomplished by stabilizing ventricular radius and increasing end-diastolic wall thickness. This results in a reduction of stress in the border zone that leads to improved contractility in this region. It is therefore postulated that the CSD decreases infarct size by halting the migration of the border zone into the infarct. Furthermore, it is postulated that stunned myocardium recovers rather than progressing toward permanent dysfunction.

Passive containment has also been used in an animal model of ischemic-dilated cardiomyopathy.\textsuperscript{21} Heart failure was created by microembolization, which results in global dysfunction and an increase in global wall stress, in contrast to the infarct model, which results in acute regional changes. These results demonstrated significantly smaller left ventricular volumes and improvement in cardiac function for CSD-treated animals compared with the controls. In addition, they reported a decrease in stretch proteins and improved Ca\textsuperscript{2+} cycling. The mechanism of action of the CSD is the same as in the acute infarct studies by decreasing wall stress (global or regional); progressive remodeling can be halted and reverse remodeling can occur.

The first Acorn CSD was placed in humans in Germany in 1999. Since that time, nearly 100 patients with dilated cardiomyopathies have had the CSD placed. So far, it has been shown to be safe. In the few patients followed for over 2 years there have been no reports of constriction developing or other major device-related complications. Although many patients have demonstrated significant improvement efficacy has yet to be demonstrated. There is an ongoing prospectively randomized multi-institutional study, in both the US and Europe, to study the effectiveness of the CSD inpatients with heart failure and dilated hearts.

There are some limitations to this study that deserve consideration. The pericardium on the CSD sheep was closed immediately postinfarct to facilitate CSD placement the following week. This can potentially effect infarct development in the first week between the 2 groups. The results, however, show that at 1-week postinfarct there is no statistical difference in absolute or relative akinetic area between the 2 groups, indicating that closing the pericardium had no observable effect. Another limitation is the lack of a sham operation at 1 week on the control animals. The effect of a sham operation, if anything, would be a negative 1 on the control group.

Additionally, MRI visible markers were not placed on the epicardium at the time of the infarct creation to delineate the baseline infarct zone. As such, we could not serially track infarct zone expansion over the course of the experiment. This would be beneficial in determining the degree of initial infarct zone expansion versus the degree of border zone pulled into the infarct area. Finally, neither pathological studies nor myocardial blood flow (perfusion) studies were performed on the hearts for infarct size determination. Correlation between the pathology, perfusion, and MRI data would be beneficial.

In conclusion, ventricular constraint using the CSD reduced infarct development secondary to acute MI. The reduction in infarct expansion by attenuation in regional wall stress would also predict a modification of the global process of ventricular remodeling. Further studies on the effect of the CSD on the process of ventricular remodeling both on a global and cellular level need to be conducted.

References

Myocardial Wall Thickness

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CSD</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-systolic we</td>
<td>0.932±0.029</td>
<td>1.205±0.047</td>
<td>0.001</td>
</tr>
<tr>
<td>End-diastolic we</td>
<td>0.908±0.026</td>
<td>1.140±0.039</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Ventricular Constraint Using the Acorn Cardiac Support Device Reduces Myocardial Akinetic Area in an Ovine Model of Acute Infarction

James J. Pilla, Aaron S. Blom, Daniel J. Brockman, Frank Bowen, Qing Yuan, Joseph Giammarco, Victor A. Ferrari, Joseph H. Gorman III, Robert C. Gorman and Michael A. Acker

*Circulation*. 2002;106:I-207-I-211
doi: 10.1161/01.cir.000032871.55215.de

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/12_suppl_1/I-207

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org/subscriptions/