Adjustable, Physiological Ventricular Restraint Improves Left Ventricular Mechanics and Reduces Dilatation in an Ovine Model of Chronic Heart Failure

Ravi K. Ghanta, MD; Aravind Rangaraj, MD; Ramanan Umakanthan, MD; Lawrence Lee, MD; Rita G. Laurence, BS; John A. Fox, MD; R. Morton Bolman III, MD; Lawrence H. Cohn, MD; Frederick Y. Chen, MD, PhD

Background—Ventricular restraint is a nontransplantation surgical treatment for heart failure. The effect of varying restraint level on left ventricular (LV) mechanics and remodeling is not known. We hypothesized that restraint level may affect therapy efficacy.

Methods and Results—We studied the immediate effect of varying restraint levels in an ovine heart failure model. We then studied the long-term effect of restraint applied over a 2-month period. Restraint level was quantified by use of fluid-filled epicardial balloons placed around the ventricles and measurement of balloon luminal pressure at end diastole. At 4 different restraint levels (0, 3, 5, and 8 mm Hg), transmural myocardial pressure (Ptm) and indices of myocardial oxygen consumption (MVO₂) were determined in control (n=5) and ovine heart failure (n=5). Ventricular restraint therapy decreased Ptm and MVO₂, and improved mechanical efficiency. An optimal physiological restraint level of 3 mm Hg was identified to maximize improvement without an adverse affect on systemic hemodynamics. At this optimal level, end-diastolic Ptm and MVO₂ indices decreased by 27% and 20%, respectively. The serial longitudinal effects of optimized ventricular restraint were then evaluated in ovine heart failure with (n=3) and without (n=3) restraint over 2 months. Optimized ventricular restraint prevented and reversed pathological LV dilatation (130±22 mL to 91±18 mL) and improved LV ejection fraction (27±3% to 43±5%). Measured restraint level decreased over time as the LV became smaller, and reverse remodeling slowed.

Conclusions—Ventricular restraint level affects the degree of decrease in Ptm, the degree of decrease in MVO₂, and the rate of LV reverse remodeling. Periodic physiological adjustments of restraint level may be required for optimal restraint therapy efficacy. (Circulation. 2007;115:1201-1210.)

Key Words: heart failure • remodeling • surgery

Ventricular restraint is a nontransplantation surgical treatment for heart failure (HF) in which both ventricles are wrapped with material designed to mechanically constrain the ventricles.¹² The intent is to provide passive end-diastolic support to constrain ventricular size without pathological diastolic restriction. Numerous studies have demonstrated that passive ventricular restraint may prevent or reverse left ventricular (LV) dilation and remodeling in HF.³⁻⁸ The precise mechanics of this, however, are not known. Our hypothesis is that ventricular restraint decreases transmural myocardial pressure (Ptm) by pressure application on the epicardium at end diastole. This hypothesis has never been documented because current restraint devices do not allow for the measurement of restraint level or Ptm.⁹,¹⁰ In addition, definitive studies that evaluate the effect of alteration of restraint level on ventricular mechanics have not yet been performed, and no criteria exist to optimize restraint therapy in a physiological manner to maximize LV performance.

Clinical Perspective p 1210

Our hypothesis is that ventricular restraint unloads the LV and reduces Ptm and myocardial oxygen consumption (MVO₂). We also hypothesize that restraint level affects therapeutic efficacy, and that, as the LV size decreases, the effective restraint level will decrease as an indication of LV improvement. To evaluate these questions, we developed an adjustable fluid-filled balloon to quantitatively apply restraint to the entire epicardial surface of both ventricles. With this new technique—quantitative ventricular restraint (QVR)—both the direct measurement of Ptm and the quantitative application of ventricular restraint are possible.
Methods

Study Design Overview

This study was divided into 2 parts. In part I, we evaluated the immediate effect of ventricular restraint on $P_{ptm}$ and indices of $MVO_2$ in normal (n=5) and HF ovines (n=5). To produce failure, ovines underwent first (D1) and second (D2) diagonal coronary artery ligation. HF, defined as an LV ejection fraction (EF) <$35\%$ and a 100% increase in LV end-diastolic volume (EDV), developed 2 months after ligation. All animals underwent placement of QVR balloons over the ventricular epicardium in a terminal study. The effect of ventricular restraint level on $P_{ptm}$, indices of $MVO_2$, systolic contractility, and systemic hemodynamics in normal and HF ovines was determined. We then identified an optimal restraint level that maximized improvement in $P_{ptm}$ and indices of $MVO_2$ and minimized adverse effects on systemic hemodynamics.

In part II, optimized QVR was applied in a 4-month longitudinal study in HF ovines to assess the long-term effect of restraint on LV EDV, EF, and the level of restraint itself. In this long-term study, 6 ovines underwent D1/D2 ligation and developed HF 2 months postligation. After the development of HF, 3 animals underwent QVR balloon implantation at the optimal restraint level and 3 animals underwent no device implantation as the control group. All animals were then followed up for an additional 2 months with serial echocardiography. In the QVR animals, restraint level was measured weekly. Throughout the study period, the QVR balloon volume was not adjusted. At termination, fluid was withdrawn from the QVR balloon and measured to verify that any changes in restraint level were not caused by a leak in the balloon.

A total of 16 adult male ovines (30 to 40 kg) were used for this study. All animals received humane care in compliance with the Guide for Care and Use of Laboratory Animals published by the National Institutes of Health (NIH publication 86-23, revised 1996). The protocol was approved by the Institutional Animal Care and Use Committee at Harvard Medical School.

Quantitative Ventricular Restraint Balloons

We designed and constructed a half-ellipsoidal balloon from medical-grade polyurethane sheets (Polyzen, Apex, NC; Figure 1). Each balloon was composed of two 1-mm-thick layers. An access line was placed between the 2 layers to allow pressure measurement inside the balloon lumen and the addition or withdrawal of fluid. The outer layer of the balloon was composed of a flexible but inelastic polyurethane layer. Because the outer layer of the balloon is inelastic but flexible, fluid introduced into the balloon lumen has only one direction of filling space—inward toward the epicardial surface. This creates a tighter wrap. Conversely, withdrawal of fluid from the balloon lumen results in a looser wrap. The balloon access line was connected to an implantable portacath (Bard Access Systems). The port was accessed with an 18-gauge Huber needle and connected to a Statham P10EZ pressure transducer (SpectraMed, Oxford, Calif). Measurement of the luminal pressure inside the balloon when the heart is largest in volume—end diastole—allows wrap tightness to be precisely quantified. At end diastole, the pressure inside the balloon is solely a function of heart volume plus the fluid volume and the mechanical properties of the outer layer. We previously verified with a dynamic testing procedure that the frequency response of the Statham transducer plus the cannula was adequate to measure fluctuations in balloon pressure to the required accuracy.11,12

In parts I and II, QVR balloons were implanted via a median sternotomy and pericardiotomy. The QVR balloon was placed over the heart to completely envelop both ventricles and secured to the atrioventricular groove. In part II, the QVR portacath was tunneled through the fifth intercostal space into the left anterior chest wall. A separate 3-cm chest wall incision was made to secure the port. The sternum and port incision were then closed in layers.

Quantitative Ventricular Restraint

Individual restraint levels were defined by the maximum pressure applied by the balloon to the epicardium, given a constant volume of saline inside the balloon. Maximum balloon pressure occurred at end diastole, the time point when the heart is largest in volume. To change restraint level, volume was added or removed from the balloon. Fluid was removed to lower the restraint level or added to raise the restraint level while balloon pressure was monitored in real time. To define an arbitrary maximum restraint level applied to a given subject without tamponade, we injected saline into the balloon until mean aortic pressure decreased by 10 mm Hg. We defined this restraint level as $P_{max}$. At restraint levels higher than $P_{max}$, tamponade physiology prevailed. We recorded data at 4 sequential restraint levels: 0 (baseline), 1/3 $P_{max}$, 2/3 $P_{max}$, and $P_{max}$.

Heart Failure Model

A postinfarction ovine model of HF, described by Moainie et al, was used.13 This model includes many of the features of ischemic human...
diographic and hemodynamic signals were digitized at 200 Hz. The thoracotomy was performed through the 4th intercostal space. D1 and D2 were identified and ligated with 4-0 polypropylene sutures. The thoracotomy was closed in layers. A single chest tube was placed to measure aortic flow. High-fidelity micromanometer (Millar Instruments, Houston, Tex) was placed in the LV and ascending aorta via the right and left femoral arteries. An 8F conductance catheter for LV volume measurement (Webster Laboratories, Baldwin Park, Calif) was placed via the right femoral vein. All electrocardiographic and hemodynamic signals were digitized at 200 Hz.

Anesthesia and Postoperative Care
For coronary ligature and balloon implantation, animals were prese- dated with Telazol (Wyeth)(4.4 mg/kg) and endotracheally intubated. Anesthesia was maintained with 1% to 2% isofluorane. A 16-gauge intravenous line was placed in the left external jugular vein for access and measurement of central venous pressure. Animals received magnesium (2 g intravenously), amiodarone (1.5 mg/kg intravenously), and lidocaine (3 mg/kg intravenously) before infarction and an infusion of amiodarone (0.01 mg/kg per min) and lidocaine (2 mg/mm) for 60 minutes afterward. Animals received buprenorphine (5 μg/kg intramuscularly every 12 hours for 2 days) for pain control and cefazolin (4 mg/kg intramuscularly every 12 hours for 2 days) for antibiotic prophylaxis.

Results
For each subject, all hemodynamic signals were recorded at 4 sequential ventricular restraint levels (0, 1/3 Pmax, 2/3 Pmax, and Pmax) over 20 beats. At each restraint level, a caval occlusion was performed with the balloon occluder. All data were collected with the ventilator off to avoid respiratory variations.

All data were analyzed on a microcomputer with MATLAB (The Mathworks, Natick, Mass). End diastole was defined as the time point in the cardiac cycle that corresponded to the R-wave on the ECG. This point corresponds closely to the closing of the mitral valve. Begin-ejection was defined as the point at which aortic flow first becomes non-zero. End systole was defined as the point at which aortic flow fell to zero after the beginning of ejection. Hemodynamic signals were ensemble-averaged over 10 beats. Pmax across the heart wall was defined as the LV pressure minus the epicardial pressure (measured by the balloon). The transmural tension-time index (TTI) was calculated by integration of Ptm with respect to time over the cardiac cycle. The end-systolic pressure-volume relationship was then calculated from the caval occlusion data, by the procedure of Kono et al.3 We then determined the transmural pressure-volume area (PVA), stroke work (area circumscribed by the pressure-volume loop), potential energy (PVA – stroke work), and mechanical efficiency (ratio of stroke work to PVA) for each restraint level.18

Serial Echocardiography
In part II, quantitative 2-dimensional transthoracic echocardiography (Cypress Acuson, Siemens Medical Solutions, Malvern, Pa) with a 3.5-MHz probe was performed preinfarction and then weekly in all animals throughout the study period. Parasternal long-axis images and short-axis images of the LV to the tips of the papillary muscles were obtained. LV EDV and end-systolic volumes were calculated by Simpson’s rule with the Cypress Acuson. LV EF was calculated as the ratio of the difference of EDV and end-systolic volume to EDV.19 All echocardiograms were analyzed by an investigator blinded to the treatment group and time.

Anesthesia and Postoperative Care
For coronary ligation and balloon implantation, animals were prese- dated with Telazol (Wyeth)(4.4 mg/kg) and endotracheally intubated. Anesthesia was maintained with 1% to 2% isofluorane. A 16-gauge intravenous line was placed in the left external jugular vein for access and measurement of central venous pressure. Animals received magnesium (2 g intravenously), amiodarone (1.5 mg/kg intravenously), and lidocaine (3 mg/kg intravenously) before infarction and an infusion of amiodarone (0.01 mg/kg per min) and lidocaine (2 mg/mm) for 60 minutes afterward. Animals received buprenorphine (5 μg/kg intramuscularly every 12 hours for 2 days) for pain control and cefazolin (4 mg/kg intramuscularly every 12 hours for 2 days) for antibiotic prophylaxis.

Pressure-Volume Analysis
In part I, 5 HF and 5 normal ovines were placed under general anesthesia and underwent QVR balloon placement. An electromagnetic aortic flow probe (Carolina Medical Electronics, King, NC) was placed to measure aortic flow. High-fidelity micromano- meters (Millar Instruments, Houston, Tex) were placed in the LV and ascending aorta via the right and left femoral arteries. An 8F conductance catheter for LV volume measurement (Webster Laboratories, Baldwin Park, Calif) was placed via the right carotid artery.24-26 A 20-ml balloon occluder was introduced into the inferior vena cava via the right femoral vein. All electrocardiographic and hemodynamic signals were digitized at 200 Hz.

TABLE 1. Baseline LV Size, Mechanics, and Energetics in Normal vs HF Ovines

<table>
<thead>
<tr>
<th></th>
<th>Normal Ovines (n=5)</th>
<th>HF Ovines (n=5)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>51.4±12.9</td>
<td>31.5±9.9</td>
<td>0.03</td>
</tr>
<tr>
<td>LV EDV, mL</td>
<td>61.1±6.6</td>
<td>123.5±23.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>31.9±11.1</td>
<td>37.7±10.7</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.12±0.89</td>
<td>3.09±0.58</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Pressure-volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Ptm, mm Hg</td>
<td>33.5±4.5</td>
<td>30.4±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>EDP,in, mm Hg</td>
<td>5.7±1.8</td>
<td>9.4±2.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Ees, mm Hg/mL</td>
<td>2.34±0.37</td>
<td>1.55±0.38</td>
<td>0.01</td>
</tr>
<tr>
<td>Volume axis intercept, mL</td>
<td>9.9±8.1</td>
<td>55.4±17.6</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Energetics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension time index, mm Hg · s</td>
<td>18.5±3.4</td>
<td>19.4±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke work, mm Hg · mL</td>
<td>1642±609</td>
<td>1246±342</td>
<td>NS</td>
</tr>
<tr>
<td>Potential energy, mm Hg · mL/beat</td>
<td>571±215</td>
<td>1042±359</td>
<td>0.046</td>
</tr>
<tr>
<td>Mechanical efficiency, %</td>
<td>73±11.5</td>
<td>54±6.3</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Ees indicates end-systolic elastance; and NS, not significant.
Part I
Baseline Differences in LV Mechanics and Energetics Between Normal and HF Ovines

Left ventricular size, mechanics, and energetics observed in the normal and postinfarction HF ovine model are tabulated in Table 1. HF ovines had enlarged hearts with depressed contractility, elevated diastolic pressures, and impaired mechanical efficiency. HF ovines demonstrated depressed LV EF (<35%) and higher LV EDV (increase of 62.1 mL or 102%). Decreased contractility was manifested by a decreased end-systolic elastance (Ees) and a rightward shift in the end-systolic pressure-volume relationship. There was no statistically significant difference in stroke volume or cardiac output. Although there was no difference in mean Ptm, Ptm was elevated throughout diastole in HF ovines compared with controls. End-diastolic Ptm was 3.7 mm Hg (65%) higher in HF ovines compared with normal ovines. In HF ovines, potential energy was 471 mm Hg-mL/beat (82%) higher secondary to increased LV volume. HF hearts were mechanically less efficient than normal hearts. No statistically significant difference existed in stroke work, PtVA, or TtTI between HF and normal ovines.

Immediate Effects of Ventricular Restraint on Left Ventricular Mechanics and Energetics

The immediate effects of ventricular restraint on LV mechanics and indices of myocardial energetics in HF and normal ovines are illustrated in Figure 3.

Transmural Myocardial Pressure

Ventricular restraint decreased Ptm throughout the cardiac cycle for both HF and normal ovines. The greatest decrease in Ptm occurred during diastole, with maximal reduction at end diastole. Figure 3A demonstrates the percent reduction in mean Ptm as a function of restraint level for normal and HF ovines. In HF ovines, mean Ptm was significantly reduced by 7%, 19%, and 35%, respectively, at each of the 3 sequentially increasing restraint levels from baseline (P<0.05). Ventricular restraint reduced Ptm equally in normal and HF ovines. Figure 3B demonstrates the percent reductions in Ptm during systole, diastole, and at end diastole in HF ovines. The greatest reduction was noted at end diastole. EDPtm decreased by 27%, 30%, and 36%, respectively, for all 3 sequentially increasing restraint levels from baseline (P<0.05).

Indices of Myocardial Energetics

Ventricular restraint decreased TtTI and PtVA in both normal and HF ovines (Figure 3, C and D). In HF ovines, TtTI decreased by 12%, 19%, and 33%, respectively, for all 3 increasing restraint levels tested from the baseline (P<0.05). In HF ovines, PtVA decreased by 20%, 27%, 51%, respectively, for all 3 increasing restraint levels from baseline (P<0.05). Ventricular restraint reduced TtTI and PtVA equally in normal and HF ovines. In HF ovines, ventricular restraint improved mechanical efficiency (Figure 3E). Mechanical efficiency improved from 55% at baseline to 63% at Pmax (P<0.05). In normal ovines, ventricular restraint had no effect on mechanical efficiency (P=0.65).
Figure 3. Short-term effect of ventricular restraint on LV mechanics and indices of myocardial energetics as a function of restraint level in normal and HF ovines. A, Mean percentage change in Ptm from baseline; B, mean percentage change in Ptm from baseline during systole, diastole, and end diastole in HF ovines; C, mean percentage change in TtTI from baseline; D, mean percentage change in PtVA from baseline; E, mechanical efficiency; F, Ees. *Statistically significant change (P<0.05) from baseline. †Statistically significant (P<0.05) difference between normal ovines (○) and HF ovines (●).
End-Systolic Elastance
In both normal and HF ovines, ventricular restraint had no immediate effect on Ees (Figure 3F). In HF ovines, Ees was 1.55 ± 0.38 mm Hg/mL at baseline and 1.61 ± 0.39 mm Hg/mL at Pmax. In normal ovines, Ees was 2.54 ± 0.37 mm Hg/mL at baseline and 2.37 ± 0.39 mm Hg/mL at Pmax. Similarly, ventricular restraint had no effect on the volume-axis intercept in both normal and HF ovines. Thus, ventricular restraint did not affect contractility in the short term as measured by end-systolic pressure-volume relationship.

Immediate Adverse Effects of Ventricular Restraint on Hemodynamics
Mean aortic pressure, heart rate, stroke volume, cardiac output, LV end-diastolic pressure, and central venous pressure in HF ovines for each restraint level are summarized in Table 2. As expected, at high restraint levels, restrictive physiology prevailed as demonstrated by a decrease in mean aortic pressure and cardiac output with a concomitant increase in LV EDP and central venous pressure. At low restraint levels, however, aortic pressure and cardiac output were unchanged.

Optimization of Ventricular Restraint Level
Increasing levels of wrap tightness caused greater decreases in Pm and indices of MVO2. Very high levels of restraint impaired systemic hemodynamics. This suggests that an optimal restraint level exists, where the reduction in Pm and MVO2 is maximized while the effect on systemic hemodynamics is minimized. Ideally, this restraint level would correct pathologically elevated stress and strain seen in HF. Figure 4A and 4B illustrate the short-term effect of ventricular restraint on LV EDPm and potential energy in HF ovines. The shaded regions in Figure 4, A and B, indicate the normal range of LV EDPm and potential energy found in ovines. Figure 4C illustrates LV EDPm and mean aortic pressure, normalized to baseline, for the 4 different restraint levels studied.

At a restraint level of 1/3 Pmax (3 mm Hg), previously elevated LV EDPm and potential energy were reduced and corrected to normal levels, whereas mean aortic pressure remained unaffected until restraint levels were greater than 1/3 Pmax. Thus, a restraint level of 1/3 Pmax (3 mm Hg) corrected abnormally elevated LV EDPm and potential energy with no effect on mean aortic pressure. These data suggest that a restraint level of 3 mm Hg is the optimal physiological restraint level for these HF ovines.

Long-Term Optimized Ventricular Restraint Therapy
QVR was then applied at the optimal therapeutic restraint level of 1/3 Pmax (3 mm Hg) in 3 HF ovines for 2 months and compared with controls that received no treatment over the same time period. Figure 5, A and B, demonstrates the effect of optimized restraint on LV EDV and LV EF in these ovines compared with controls. At the time of QVR balloon implantation, both groups demonstrated dilated cardiomyopathy, with increased LV EF and depressed LV EF. Over the subsequent 2-month period, QVR significantly decreased LV EDV from 130 ± 22 mL to 91 ± 18 mL (−30%, P < 0.05), and improved LV EF from 27 ± 3% to 43 ± 5% (P < 0.05). In contrast, control animals developed increasing measures of HF, which included an increase of LV EDV from 113 ± 19 mL to 168 ± 7 mL (49%, P < 0.05) and a decrease of LV EF from 33 ± 2% to 19 ± 8% (P < 0.05). LV EDV was 77 mL lower (−90%, P < 0.05) and LV EF was 24% higher (P < 0.05) in QVR ovines compared with controls. In QVR ovines, LV EDV decreased 21 days after the initiation of QVR therapy (P < 0.05), and LV EF improved 42 days after initiation of QVR therapy (P < 0.05). Furthermore, restraint level decreased as the heart decreased in size (Figure 5C). As restraint level decreased, reverse remodeling slowed, as measured by the rate of change of LV EDV over time.

Discussion
Previous studies have demonstrated the potential for ventricular restraint to prevent and reverse pathological LV remodeling.1–8,20,21 To date, no study has evaluated LV mechanics in restraint or the effect of adjustable restraint. Current ventricular restraint techniques, such as the Acorn Cardiac Support Device (Acorn Cardiovascular, St. Paul, Minn) and the Paracor (Paracor Medical Systems, Sunnyvale, Calif), do not allow for either the quantitative adjustment of restraint level or the measurement of Pm.3,10 A standard for wrap tightness does not exist. Surgeons are instructed to apply the Acorn Cardiac Support Device in such a way that it fits not too loosely and not too tightly, but “snugly.” Once wrapped at the initial procedure, the restraint wrap is constant and unchanging even as the heart undergoes reverse remodeling.

---

**TABLE 2. Adverse Effects of High Levels of Restraint on Hemodynamics**

<table>
<thead>
<tr>
<th>Restraint Level</th>
<th>MAP, mm Hg</th>
<th>HR, bpm</th>
<th>SV, mL</th>
<th>CO, L/min</th>
<th>LV EDP, mm Hg</th>
<th>CVP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>51.5 (±5.9)</td>
<td>84 (±14)</td>
<td>37.7 (±10.7)</td>
<td>3.1 (±0.6)</td>
<td>10.6 (±4.6)</td>
<td>14.1 (±7.9)</td>
</tr>
<tr>
<td>1/3 Pmax</td>
<td>51.5 (±7.2)</td>
<td>86 (±13)</td>
<td>32.7 (±7.4)</td>
<td>2.8 (±0.5)</td>
<td>10.0 (±3.6)</td>
<td>13.3 (±6.9)</td>
</tr>
<tr>
<td>2/3 Pmax</td>
<td>48.5 (±7.2)*</td>
<td>87 (±11)</td>
<td>31.1 (±4.7)</td>
<td>2.7 (±0.6)</td>
<td>11.2 (±5.4)</td>
<td>15.5 (±7.1)</td>
</tr>
<tr>
<td>Pmax</td>
<td>43.0 (±6.9)*</td>
<td>87 (±10)</td>
<td>26.0 (±5.1)*</td>
<td>2.3 (±0.7)*</td>
<td>11.7 (±4.6)*</td>
<td>18.5 (±9.7)*</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; and CVP, central venous pressure. *Statistically significant change from baseline (P<0.05).
To address these limitations, we used a half-ellipsoid, fluid-filled epicardial balloon. Restraint therapy ultimately acts on the heart via application of either shear stresses (tangential forces) or normal stresses (perpendicular forces) to the epicardium. Because neither is quantified with current restraint therapy, a separation of wrap mechanics from ventricular mechanics is neither possible nor measurable. The QVR balloon essentially introduces a fluid layer as the sole means to implement ventricular restraint. Because fluids by definition cannot sustain shear stresses, the QVR balloon affects ventricular restraint by normal forces only. Other restraint devices apply some degree of shear stress. Shear stress does not contribute to reverse remodeling but may contribute to cardiac restriction. The QVR balloon thus provides a methodology to definitively understand and quantify the effect of ventricular restraint by measurement of those normal forces (the only stresses exerted) on the epicardium.

With this technique, we demonstrated that ventricular restraint decreases $P_{tm}$ throughout the cardiac cycle. The greatest reduction in $P_{tm}$ occurred during diastole, with the maximum reduction at end diastole. The largest reduction in $EDP_{tm}$ occurred when restraint level was increased from 0 (baseline) to 1/3 $P_{max}$ (3 mm Hg). As restraint level increased, further decreases in $P_{tm}$ were more pronounced during systole with relatively modest further reductions during diastole. Thus, at low restraint levels, ventricular restraint affected $P_{tm}$ primarily during diastole. At high restraint levels, ventricular restraint acted primarily during systole to decrease $P_{tm}$, consistent with early restrictive physiology.

Important concerns with restraint therapy are cardiac restriction and impairment of coronary blood flow. The maximum applicable restraint level will be limited by the restrictive effect of the restraint device, primarily on the low-pressure right ventricle. It is well known that elevated epicardial pressure impairs right ventricular filling and atrioventricular coupling. In the present study, high levels of restraint (8 mm Hg) decreased cardiac output and increased central venous pressure. At low restraint levels (3 mm Hg), no evidence of cardiac restriction was seen (Table 2). Previous studies have demonstrated that elevated pericardial pressure also decreases coronary blood flow through either a reduction of coronary perfusion pressure or an increase in coronary vascular resistance. This effect, however, primarily only occurs in low cardiac output states or very high pericardial pressures (>15 mm Hg). Although we did not measure coronary blood flow, at our low levels of epicardial pressure we found no evidence of significant ischemia, as contractility was not impaired and LV function improved. Excessive ventricular restraint may impair coronary blood flow and be an important concern, particularly in patients with underlying coronary artery disease and subclinical myocardial ischemia.

Because wall stress is directly proportional to $P_{tm}$, these results suggest that ventricular restraint reduces wall stress. If ventricular restraint reduces wall stress, a major determinant

![Figure 4. Optimization of ventricular restraint level. A, End-diastolic $P_{tm}$ in HF ovines (○) at 4 different restraint levels. B, Potential energy in HF ovines at 4 different restraint levels. In A and B, the shaded region represents the range in normal ovines. C, Normalized end-diastolic $P_{tm}$ and mean aortic pressure at the 4 different restraint levels. At the optimal level of restraint pathologically elevated end-diastolic $P_{tm}$ and potential energy are corrected to the normal level with no affect on mean aortic pressure. *Statistically significant ($P<0.05$) change from baseline.]
of MVO₂, one would expect to see a decrease in O₂ uptake. In this study, we show that MVO₂ indices are acutely decreased secondary to a decrease in Pₘ and LV unloading. Because of higher filling volumes, dilated cardiomyopathic hearts have higher potential energy (or internal work) compared with normal controls. These data show that in cardiomyopathy, ventricular restraint unloads the LV and decreases potential energy more significantly than stroke work. Mechanical efficiency is thus improved [stroke work/(stroke work + potential energy)] in cardiomyopathic hearts. Conversely, in normal hearts with typical LV loading, ventricular restraint decreases potential energy and stroke work equally and thus has no effect on mechanical efficiency.

Comparing normal to cardiomyopathic hearts, we found that ventricular restraint decreased Pₘ, T,Ti, and P,V,A equally at the levels we tested. We conclude that LV size, load, and contractility were not determinative factors in the reduction of Pₘ and MVO₂ at the restraint levels we tested. We also conclude that the mechanical effect of restraint is primarily determined by wrap mechanics and not by the contractile or mechanical properties of the heart itself. Standardization of wrap mechanics should thus allow for standardization of therapy for patients.

An interesting question is whether optimization to the highest physiological restraint level may improve therapeutic efficacy. By application of optimal restraint over a 2-month period, we demonstrated a 30% reduction in LV EDV compared with baseline in ovines. Progressive LV dilatation was prevented and reversed, as LV EDV was 90% higher in controls after 2 months. In comparison, Saveedra et al found a 19 ± 4% reduction in LV EDV over 6 months in a canine model of HF that used the Acorn Cardiac Support Device. Other studies in animal models demonstrated prevention rather than reversal of LV dilation. In human studies, modest improvements in LV EDV have been found. Reverse remodeling may be dependent on restraint level. At low restraint levels, ventricular restraint may provide simple containment. At such levels of restraint, progression of disease may be halted but reversal of dilatation may not necessarily be enabled. Our results suggest that at higher restraint levels ventricular restraint contains and unloads the LV, which leads to decreased LV size. The greater decrease in LV EDV seen in this study compared with previous studies may be caused by the optimized restraint level.

The data demonstrate that restraint level is not constant as the LV remodels. We found that pressures measured in the QVR balloon decreased with time (Figure 5C). As the LV undergoes reverse remodeling and becomes smaller, the ventricular wrap stays constant. Our conclusion is that a smaller LV effectively loosens the ventricular restraint wrap and restraint level decreases. In addition, as the restraint level decreased, reverse remodeling slowed (as measured by the rate of change of LV EDV over time) (Figure 5C). This finding suggests that restraint level is an important determinant of reverse remodeling efficiency. To maximize therapeutic efficacy, periodic adjustment of wrap tightness to maintain the most effective physiological restraint level may be beneficial.

Figure 5. Efficacy of optimized QVR. A, LV EDV in treatment ovines (●) and control HF ovines (○). B, LV EF in treatment and control HF ovines. C, Restraint level and rate of change of LV EDV (dLV EDV/dt) over a 2-month treatment period. *Statistically significant change (P < 0.05) from time 0 (time of QVR balloon implantation). †Statistically significant difference (P < 0.05) between treatment and control HF ovines.
With present devices, the restraint wrap is constant and unchanging, even as the heart undergoes reverse remodeling. With a quantitative technique, patient-specific restraint levels might be identified at the time of restraint device implantation. Postoperatively, restraint level could be measured and adjusted via a portacath to maintain the optimal level. Restraint level could be adjusted as the LV remodels. Periodic assessment of ventricular mechanics and filling in real time as wrap tightness is adjusted noninvasively could be performed via echocardiography to ensure the most physiologically appropriate restraint level.

This study has some important limitations. We used 16 ovines in this study (10 in part I and 6 in part II). Only 3 underwent long-term QVR implantation. Despite this small sample size, we still had sufficient power to identify a significant difference in LV EDV and LV EF in control versus QVR ovines. The analysis of part I was performed in a time-limited terminal experimental preparation under general anesthesia. General anesthesia diminishes compensatory adrenergic and neurohormonal responses, such as a compensatory rise in heart rate with a significant fall in blood pressure observed at marked levels of restraint. These responses may alter the optimal restraint level in conscious subjects. In addition, we used pressure-volume analysis to determine the short-term effects of restraint on LV mechanics, energetics, and mechanical efficiency. Although these techniques are widely validated and allow determination of the short-term effects of restraint, the effect of restraint on wall stress will change over time as the LV changes in size, shape, and mass. More sophisticated techniques, such as cardiac magnetic resonance imaging, that take into account 3-dimensional geometry will be required to quantitatively evaluate the long-term effects of restraint on wall stress.

In summary, we have demonstrated a new quantitative technique for the measurement and application of adjustable ventricular restraint. With use of QVR in a postinfarction ovine model of HF, our results demonstrate that ventricular restraint decreases $P_{L}$ and $MV_{O2}$ and improves mechanical efficiency. Improvements in $P_{L}$, $MV_{O2}$, and mechanical efficiency were dependent on wrap tightness. With QVR, an optimized therapeutic restraint level was identified to restore physiology and maximize reductions in $P_{L}$ and $MV_{O2}$ and to minimize the effects on systemic hemodynamics. Optimized ventricular restraint reversed pathological LV dilation and improved LV function. Restraint level, however, decreased over time as the LV became smaller, and reverse remodeling slowed until a new steady-state LV volume was achieved. Clinically, interval adjustment of restraint to the optimal physiological level may be required to maintain maximum therapeutic benefit.

Sources of Funding
This work was supported by Brigham and Women’s Hospital, Department of Surgery (Dr Chen), Cardiac Surgery Research Fund (Dr Cohn, Dr Bolman); by the American Association for Thoracic Surgery, Andrew G. Morrow Scholarship (Dr Chen); by the National Institutes of Health F32 National Research Service Award (Dr Ghanta); and by the Center for Integration of Medicine and Innovative Technology (CIMIT; Dr Chen).

Disclosures
The Brigham and Women’s Hospital has patent rights on the device described in this article.

References
Heart failure is a deadly epidemic with few therapeutic options. Ventricular restraint therapy is a promising nontransplantation surgical option for heart failure in which the heart is wrapped with passive material to prevent adverse dilatation. Numerous studies have demonstrated that restraint reverses left ventricular dilatation and promotes reverse remodeling in animal models and human patients. This includes the largest prospective trial of any surgical procedure for heart failure, the ACORN Clinical Trial, which involved 300 patients. Despite these promising results, the science behind restraint remains sparse. With current devices, restraint level is neither adjustable nor measurable. Surgeons’ instructions are to place the device on the heart “snugly.” Questions remain as to the exact levels that would give a salutary effect but would not cause any hemodynamic compromise by restriction or tamponade. Because restraint levels are currently not measurable, we lack a rational approach to the application of this therapy. The findings in this study establish the need for a measurable and adjustable technique to apply ventricular restraint. They show that improvements in ventricular mechanics and energetics correlate to the level of restraint therapy applied. As the heart shrinks, the restraint level also decreases and the rate of reverse remodeling slows. The clinical implications of these findings are that such a technique is necessary to optimize reverse remodeling and that periodic adjustments of restraint level may be required for continued benefit. Therapy may then be customized for each patient on the basis of rational criteria and decreased if restrictive effects are noted. Although further study is required, adjustable measurable restraint therapy may represent an important clinical option for patients with end-stage heart failure.
Adjustable, Physiological Ventricular Restraint Improves Left Ventricular Mechanics and Reduces Dilatation in an Ovine Model of Chronic Heart Failure
Ravi K. Ghanta, Aravind Rangaraj, Ramanan Umakanthan, Lawrence Lee, Rita G. Laurence, John A. Fox, R. Morton Bolman III, Lawrence H. Cohn and Frederick Y. Chen

_Circulation._ 2007;115:1201-1210; originally published online March 5, 2007;
doi: 10.1161/CIRCULATIONAHA.106.671370
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 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/115/10/1201_