Optimized ventricular restraint therapy: Adjustable restraint is superior to standard restraint in an ovine model of ischemic cardiomyopathy

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Objective: The effects of ventricular restraint level on left ventricular reverse remodeling are not known. We hypothesized that restraint level affects the degree of reverse remodeling and that restraint applied in an adjustable manner is superior to standard, nonadjustable restraint.

Methods: This study was performed in 2 parts using a model of chronic heart failure in the sheep. In part I, restraint was applied at control (0 mm Hg, n = 3), low (1.5 mm Hg, n = 3), and high (3.0 mm Hg, n = 3) levels with an adjustable and measurable ventricular restraint (AMVR) device. Restraint level was not altered throughout the 2-month treatment period. Serial restraint level measurements and transthoracic echocardiography were performed. In part II, restraint was applied with the AMVR device set at 3.0 mm Hg (n = 6) and adjusted periodically to maintain that level. This was compared with restraint applied in a standard, nonadjustable manner using a mesh wrap (n = 6). All subjects were followed up for 2 months with serial magnetic resonance imaging.

Results: In part I, there was greater and earlier reverse remodeling in the high restraint group. In both groups, the rate of reverse remodeling peaked and then declined as the measured restraint level decreased with progression of reverse remodeling. In part II, adjustable restraint resulted in greater reverse remodeling than standard restraint. Left ventricular end diastolic volume decreased by 12.7% ($P = .005$) with adjustable restraint and by 5.7% ($P = .032$) with standard restraint. Left ventricular ejection fraction increased by 18.9% ($P = .014$) and 14.4% ($P < .001$) with adjustable and standard restraint, respectively.

Conclusions: Restraint level affects the rate and degree of reverse remodeling and is an important determinant of therapy efficacy. Adjustable restraint is more effective than nonadjustable restraint in promoting reverse remodeling. (J Thorac Cardiovasc Surg 2013;145:824-31)

Ventricular restraint therapy is a nontransplant surgical treatment for heart failure in which both ventricles are wrapped with prosthetic material.[1,2] The intent is to mechanically constrain the ventricles without causing excessive diastolic constriction or tamponade. Numerous studies have demonstrated that restraint not only prevents further pathologic left ventricular (LV) dilatation but also induces reverse remodeling at both the molecular and systemic levels.[3-6]

Restraint devices tested in clinical trials, however, do not allow for either the measurement or adjustment of wrap tightness; the restraint level is not quantified. Such restraint devices are applied around the heart at a subjective level of tightness. The influence of restraint level on therapy efficacy is thus unclear. To address this issue, we developed and described a new technique—adjustable and measurable ventricular restraint (AMVR)—in which a fluid-filled epicardial balloon is placed around the heart.[7] By use of a fluid layer to effect restraint, adjustability and measurability of therapy was achieved.

We demonstrated with AMVR that restraint decreases LV transmural myocardial pressure and indices of myocardial oxygen consumption in a restraint level–dependent manner.[7] Progressively higher levels of restraint will ultimately cause tamponade, however, and we showed that this tamponade physiology is secondary to (RV) constriction only.[8] When restraint is applied in a fixed, constant manner, our results demonstrate that the rate of reverse remodeling slows as the heart shrinks and undergoes reverse remodeling. These findings suggest that the interplay between restraint

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Funded by Brigham and Women's Hospital, Department of Surgery (to F.Y.C.), Brigham and Women's Hospital, Cardiac Surgery Research Fund (to R.M.B.), J. Paul Finnegan Endowment in Cardiac Surgery Research (to F.Y.C.), National Institutes of Health T32HL076130 (to L.S.L.), F32HL080904 (to R.K.G.), F32HL104923 (M.K.), RO1HL091157 (to R.Y.K.), RO1HL10378 (to R.L.), RO1HL102791 (to R.L.), RO1HL102786 (to R.L.), and RO1HL090862 (to F.Y.C.). The Brigham and Women's Hospital has patent rights on the device described in this manuscript.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Jan 19, 2012; revisions received April 9, 2012; accepted for publication May 9, 2012; available ahead of print June 14, 2012.

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0022-5223/$36.00

doi:10.1016/j.jtcvs.2012.05.018

Abbreviations and Acronyms

AMVR = adjustable and measurable ventricular restraint
BNP = brain natriuretic peptide
CMR = cardiac magnetic resonance
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
LV = left ventricular
MMP-2 = myocardial matrix metalloproteinase-2
RV = right ventricular

therapy and ventricular remodeling is a dynamic process that may require periodic adjustment of restraint level to maintain therapeutic efficacy.

In this study, we seek to definitively investigate the role that restraint level plays in inducing reverse remodeling. Although our previous studies delineated the relationship between restraint level and acute ventricular mechanical indices, these were not long-term in vivo studies evaluating the relationship between restraint level and reverse remodeling itself. For the present study, we hypothesized that (1) the initial, or starting, restraint level is a key determinant of the degree of reverse remodeling in standard, nonadjusted restraint therapy and (2) restraint therapy applied in an optimized, adjustable manner is superior to restraint applied in a fixed, nonadjustable manner in promoting reverse remodeling.

METHODS

Study Design Overview

This study was performed in 2 parts: (1) a 4-month study investigating the effects of different *initial* restraint levels on reverse remodeling and (2) a 4-month study comparing optimized, adjustable restraint therapy to standard, nonadjustable restraint therapy.

In part I, 9 sheep underwent coronary artery ligation through a left thoracotomy to develop heart failure. Animals were then divided into 3 equal groups: control (no restraint), low restraint (1.5 mm Hg), and high restraint (3.0 mm Hg). Nine total sheep were used. The control group had no restraint device implanted. Low and high restraint groups underwent reoperative median sternotomy with implantation of the AMVR device. The restraint device was filled with fluid to achieve the desired restraint levels (1.5 mm Hg in the low group and 3.0 mm Hg in the high group). Restraint level was defined by the measured balloon luminal pressure at end-diastole. The levels chosen were based on our previous results with this animal model demonstrating beneficial changes at these restraint levels. Restraint levels greater than 3.0 mm Hg were not tested because our previous results demonstrated decreased cardiac output with impaired RV filling at those higher levels, suggesting that 3.0 mm Hg is the optimal restraint level for this particular model.[7,8]

After device placement, all subjects were followed up for 2 months with serial transthoracic echocardiography. The volume of fluid in the AMVR device was not altered to reflect the unchanging nature of clinical devices. Restraint level was measured weekly throughout the study period to assess the effect of reverse remodeling on restraint level. A terminal experiment was performed to obtain and analyze myocardial tissue samples for molecular markers of remodeling. The long-term effects of the initial starting restraint level on ventricular volumes and the level of restraint itself were then measured and compared.

In part II, 12 sheep underwent coronary artery ligation, and heart failure developed by 2 months postoperatively in all of them. Animals were then divided into 2 groups: standard, nonadjustable restraint (n = 6) and optimized, adjustable restraint (n = 6). All sheep underwent reoperative median sternotomy for implantation of the assigned treatment device. In the standard restraint group, a polypropylene mesh was wrapped around the heart to simulate unchanging restraint devices. In the adjustable restraint group, AMVR devices were implanted and set at a restraint level of 3.0 mm Hg. This level was chosen because our previously published studies showed this to be the optimal restraint level at which beneficial changes in ventricular mechanical indices are maximized while adverse systemic hemodynamic effects are minimized in this particular sheep model.[7,8]

All 12 subjects were then followed up for 2 months with serial cardiac magnetic resonance (CMR) imaging. In the adjustable restraint group, the restraint level was measured biweekly and the volume in the restraint device adjusted to maintain a restraint pressure of 3.0 mm Hg throughout the study duration. No postoperative measurement or manipulation of restraint level was possible in the fixed restraint group simulating standard clinical restraint. Blood samples were obtained biweekly in all animals to assess for plasma markers of remodeling. A terminal experiment was performed to obtain and analyze myocardial tissue samples for molecular markers of remodeling.

A total of 21 (9 in part I, 12 in part II) adult male sheep (30-40 kg) were used for the 2 parts of 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 no. 86-23, revised 1996). The protocol was approved by the Institutional Animal Care and Use Committee of Harvard Medical School.

The specific techniques and methodologies used are described below.

Heart failure model. An ovine model of postinfarction heart failure involving ligation of the first and second diagonal coronary arteries was used.[7-9] Heart failure, defined as an LV ejection fraction (EF) less than 40% and a 100% increase in LV end-diastolic volume (EDV) from preoperative baseline, was confirmed by either echocardiography or CMR imaging.

Adjustable and measurable ventricular restraint. The AMVR device is a half-ellipsoidal balloon constructed from medical-grade polyurethane sheets (Polyzen, Inc, Apex, NC) and has been described previously.[7] Each balloon is composed of 2 layers. An access line placed between the 2 layers allows for pressure measurement inside the balloon lumen and the addition or withdrawal of fluid. Because the outer layer of the balloon is relatively nonstretchable, fluid introduced into the balloon lumen has only 1 direction of filling space—inward toward the heart, thereby creating a tighter wrap. Conversely, withdrawal of fluid from the balloon lumen creates a looser wrap. The device is placed around the heart via median sternotomy and sutured to the atrioventricular groove such that both ventricles are covered. The balloon access line is connected to an implantable catheter (Port-a-Cath; Bard Medical, Covington, Ga), which is placed in the chest wall. The port can be accessed with an 18-gauge Huber needle and connected to a Statham P10EZ pressure transducer (SpectraMed, Oxford, Calif). Measuring the pressure within the balloon when the heart is largest in size—end-diastole—allows wrap tightness (or restraint level) to be precisely quantified. Restraint level is changed by adding or removing fluid from the balloon while luminal pressure is monitored in real time.

Standard, nonadjustable ventricular restraint. Standard, fixed restraint intended to simulate clinically tested restraint devices was achieved with a polypropylene mesh wrap (Ethicon, Inc, Somerville, NJ). A median sternotomy was performed and the mesh was placed around the heart in accordance with guidelines used for placement of the Acorn CorCap cardiac support device (Acorn Cardiovascular, Inc, St Paul,