Right Heart Failure: An Ischemic Model and Restraint Therapy for Treatment

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Background. Right heart failure is poorly understood and treated. In left heart failure, ventricular restraint can reverse pathologic left ventricular remodeling. The effect of restraint in right heart failure, however, is not known. We hypothesize that ventricular restraint can be applied selectively to the right ventricle (RV) to promote RV reverse remodeling.

Methods. Right heart failure was induced by right coronary artery ligation in a sheep model. Eight weeks later, a saline-filled epicardial balloon was placed around the RV surface for restraint. Restraint level was defined by measuring balloon luminal pressure at end-diastole. Maximum balloon pressure was determined by the amount of balloon pressure required to decrease systemic mean arterial pressure by 10 mm Hg. We determined end-diastolic transmural myocardial pressure, indices of myocardial oxygen consumption, and RV diastolic compliance at 4 different restraint levels.

Results. After coronary ligation, RV ejection fraction (EF) decreased from 0.574 ± 0.04 to 0.362 ± 0.03 (p < 0.05). End-diastolic RV volume increased from 70.8 mL/m² ± 9 to 82.2 mL/m² ± 7 (p < 0.05) by magnetic resonance imaging. After application of restraint to the RV only, RV transmural pressure decreased significantly by 27%. Greater levels of restraint also improved RV EF (0.347 ± 0.06 to 0.473 ± 0.05) but did not change RV end-diastolic volume.

Conclusions. A model of ischemic right heart failure was successfully created. Selective RV restraint results in improved mechanical efficiency, decreased wall stress, and improved EF. The benefits of restraint in right heart failure warrant further investigation.

Accepted for publication Sept 23, 2013.


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Right heart failure (RHF) is an important clinical entity affecting half a million Americans. It is increasingly recognized as its own disease entity, one that has a different pathophysiologic basis from left heart failure [1–4]. Right heart failure has a high morbidity and mortality, and is associated with impaired functional status, arrhythmia, and premature death [1, 3].

With few therapeutic options, RHF treatment strategies are limited. Ventricular restraint is a nontransplant surgical treatment for heart failure in which the entire epicardial surface is wrapped with a prosthetic material [5]. Previous work from our group demonstrated that ventricular restraint can reverse the pathologic ventricular remodeling associated with left heart failure [5–9]. However, in the setting of a normal right ventricle (RV) and failing left ventricle (LV), restraint applied to both ventricles has no beneficial effect on the RV [8]. At higher restraint levels (where LV compliance was unchanged), effective RV compliance diminished and ultimately impaired RV filling. At those levels, however, the LV continued to receive therapeutic benefit, as evidenced by decrease in LV transmural pressure (Ptm) without any adverse change in effective LV compliance (Cv) [8]. We concluded that the thin-walled RV is more susceptible to the effects of external epicardial forces causing tamponade and should be considered separately.

We hypothesized that in the setting of RHF, selective RV restraint (ie, restraint applied solely to the RV epicardial surface) would result in acutely improved RV mechanics. In this study we sought to do the following: (1) create a model of ischemic RHF; and (2) determine whether ventricular restraint can be applied solely to the RV with acute therapeutic benefit.

Material and Methods

Study Overview

This study was performed in 3 parts. (1) Baseline cardiac magnetic resonance imaging (cMRI) established normal values of right heart function and size. (2) Right coronary artery (RCA) ligation was performed and ischemic RHF developed over 8 weeks. The cMRI reevaluated RV heart function and size. (3) Acute, terminal studies evaluated the effects of ventricular restraint on RV Ptm, indices of myocardial oxygen consumption (MVCO2), compliance,
and hemodynamics in both RHF sheep and a normal, non-heart failure control group.

A total of 10 adult male sheep (weight range 40 to 45 kg) were used. All animals received humane care in compliance with the “Guide for Care and Use of Laboratory Animals” (www.nap.edu/catalog/5140.html) published by the National Institutes of Health. The protocol was approved by the Institutional Animal Care and Use Committee at Harvard Medical School.

Experimental Design

BASELINE CARDIAC MAGNETIC RESONANCE IMAGING (cMRI). Five normal adult male sheep underwent cMRI to evaluate for baseline ejection fraction (EF), end-diastolic volume, and end-diastolic volume (EDV). Imaging was performed with a 3-tesla magnetic resonance scanner (Signa CV/I; General Electric Healthcare, Milwaukee, WI). All acquisitions were obtained with an 8-element cardiac phased-array surface coil with the animal in the lateral decubitus position under general anesthesia and ventilatory support. Peripheral pulse gating was used to minimize cardiac and respiratory motion. After cardiac localization, cine imaging of cardiac function was performed with cine steady-state free precession fast-gradient echocardiographic imaging in 8 to 12 parallel short-axis slices (8-mm thickness, 0-mm skip) covering the entire heart and 3 radial long-axis LV planes. Typical cine imaging parameters included repetition time of 3.4 ms, echo time of 1.2 ms, flip angle of 45 degrees, number of excitations of 1, in-plane spatial resolution of 1.5 mm by 1.5 mm, and views per segment of 12, providing a temporal resolution of approximately 40 ms.

Cine function analysis was performed off-line (QMASS 7.1; Medis Medical Imaging Systems, Inc, Leiden, The Netherlands). The cardiac phase with the largest RV cavity size was considered end-diastole, and that with the smallest RV cavity size as end-systole. A single experienced observer manually traced the endocardial contours of the RV and LV to determine the ventricular chamber volumes at end-diastole and end-systole. Papillary muscles were included in the ventricular cavity volume. For the RV basal slice in both end-diastole and end-systole, if the pulmonary valve was visible, only the portion of the volume surrounded by trabeculated myocardium below the valve was considered ventricle and included. For the inflow portion of the RV, blood volume was excluded from the RV volume if the surrounding wall was thin and non-trabeculated; this was considered to be part of the right atrium. The RV EF and LV EF were computed according to the Simpson rule as the difference between EDV and end-systolic volume as a percentage of EDV.

Selective RV Quantitative Ventricular Restraint

Current clinical restraint devices do not allow for measurement or adjustment of wrap tightness. To address this limitation, our group previously developed and described restraint therapy that is measurable and adjustable [5–8]. Quantitative ventricular restraint (QVR) was achieved with a fluid-filled epicardial balloon placed around both ventricles and secured to the atioventricular groove (Fig 1) [5–8]. The outer layer of the balloon is flexible but inelastic while the inner layer is redundant. An access line connected to the balloon lumen allows for fluid volume in the balloon to be adjusted. Because the outer layer of the balloon is inelastic, fluid introduced into the balloon lumen can only fill space inwardly towards the heart, thereby creating a tighter wrap. Conversely, withdrawing fluid loosens the wrap. By measuring balloon luminal pressure at end-diastole when the heart is largest in volume, the precise quantification of wrap tightness and restraint level is possible. Restraint level is changed by adding or withdrawing fluid from the balloon. Intraluminal balloon pressure can be monitored in real time.

For this study, the QVR device was adapted to fit over the RV surface only, i.e., selective RV QVR, leaving the LV exposed and unrestrained. Eight different QVR devices were pre-fabricated to correspond to anticipated varying geometries of the dilated RV specific to each subject. The device was sewn in over the RV with interrupted 4-0
Ethibond sutures placed along the atrioventricular groove of the RV, along the left side of the left anterior descending coronary artery, and along the left side of the posterior descending coronary artery.

Pressure-Volume Analysis

All sheep that developed RHF from RCA ligation were placed under general anesthesia and underwent selective RV QVR balloon placement by median sternotomy. Additionally, a control group of five sheep with normal heart function also underwent placement of the QVR device. Each QVR device was tailored to specifically fit the dilated post infarction right ventricle or the normal, nondilated right ventricle in the control group. Prior to balloon placement, a 16-gauge intravenous line was placed in the left external jugular vein for access and measurement of central venous pressure. An electromagnetic flow probe (Carolina Medical Electronics, King, NC) measured aortic flow. High-fidelity micromanometers (Millar Instruments, Houston, TX) were placed in the LV, RV, and aorta. An 8F conductance catheter for volume measurement (Webster Laboratories, Baldwin Park, CA) was placed in the RV (Fig 2). Next, selective RV QVR balloons were placed as described above. All electrocardiographic and hemodynamic signals were sampled at 200 Hz. We defined the maximal pressure tested \( P_{\text{max}} \) in our study as the level at which mean arterial pressure (MAP) fell by 10 mm Hg, indicative of tamponade physiology. This was consistent with the approach taken in prior studies performed by our working group. In our animal model, \( P_{\text{max}} \) varied depending on the degree of RHF that developed. For each subject, all signals were recorded at 4 sequential restraint levels (\( P_{\text{max}} \), 2/3 \( P_{\text{max}} \), 1/3 \( P_{\text{max}} \), and 0). All data were collected for 20 beats with the ventilator off to avoid respiratory variations. The heart rate varied among animals (80 to 140 beats per minute) and tended to increase with higher restraint level, but no more than 10 beats per minute above baseline. At each restraint level, an inferior vena cava occlusion was performed to determine preload-independent RV end-systolic elastance and \( C_d \) values (compliance was calculated as the linear slope of the end-diastolic pressure-volume relationship at each specific restraint level pressure that we tested.)

Data were analyzed on a microcomputer with the program MATLAB (The MathWorks, Natick, MA). End-diastole was defined as the time in the cardiac cycle that corresponded to the R wave on the electrocardiogram. Begin-ejection was the point at which pulmonary flow became nonzero, whereas end-systole was the point when pulmonary flow became 0 after begin-ejection. The \( P_{\text{tm}} \) across the heart wall was defined as the ventricular pressure minus the epicardial pressure (as measured by the balloon). Average RV \( P_{\text{max}} \) was 8.4 ± 2.1 mm Hg. The RV transmural tension-time index (TTI), a measure of ventricular work, was calculated by integrating \( P_{\text{max}} \) with respect to time across the cardiac cycle. The RV end-systolic pressure-volume relationship and the end-systolic pressure-volume relation...
The diastolic pressure-volume relationship were determined from the caval occlusion data [10]. The transmural pressure-volume area was calculated for each restraint level.

**Anesthesia and Postoperative Care**

Animals were sedated with tiletamine hydrochloride and zolazepam hydrochloride (Telazol, 6 mg/kg intramuscularly), and endotracheally intubated. Anesthesia was maintained with 1% isoflurane. Animals undergoing survival surgery received both buprenorphine (5 µg/kg intramuscularly) for pain control and cefazolin (3 mg/kg intramuscularly) for antibiotic prophylaxis every 12 hours postoperatively for 2 days.

**Statistical Analysis**

All data are reported as means and standard deviations. Differences between baseline measurements and measurements at subsequent times were compared using analysis of variance with repeated measures.

**Results**

**Baseline Studies**

Average baseline RV EF was 0.574 ± 0.04. Average RV end-diastolic volume was 70.8 mL ± 9. Average RV end-systolic volume was 34.5 mL ± 4. Average stroke volume was 41.2 mL ± 5.

**Acute RCA Infarct Studies**

Results from acute RCA infarct studies are shown in Table 1. Eight out of 10 animals survived ligation of the right coronary artery. Two intraoperative deaths occurred secondary to ventricular fibrillation. All 8 surviving animals underwent repeat cMRI at 8 weeks post infarct. Seven of the 8 animals developed RHF as defined as an RV EF of less than 0.40. Average RV EF after 8 weeks was 0.362 ± 0.03. This represents a 0.369 decrease from baseline (p < 0.05). A dramatic increase in RV size was observed 8 weeks after infarction (Fig 3). Average RV EDV was 82.2 mL ± 7, representing a 16.1% increase from baseline (p < 0.05). Average RV end-systolic volume was 46.4 mL ± 6, representing a 25.6% increase from baseline (p < 0.05). Average stroke volume was 31.1 mL ± 4, representing a 24.1% decrease from baseline (p < 0.05).

**Acute Right Ventricular Restraint Device Studies**

The MAP, RV P<sub>max</sub>, RV C<sub>es</sub>, RV end-systolic elastance, and indices of MVO<sub>2</sub> (including stroke work and tension-time index) for each restraint level on the RV are summarized in Table 2 for heart failure sheep and Table 3 for normal sheep. In the acute heart failure model, RV P<sub>max</sub>, tension-time index, pressure-volume area, and stroke work decreased to a greater degree as restraint level was increased to P<sub>max</sub> (27%, 47%, 39%, and 49% reductions compared with baseline, respectively). Higher restraint levels improved RV EF from a baseline of 0.347 ± 0.06 to a P<sub>max</sub> value of 0.473 ± 0.05 but left RV EDV relatively unchanged. In non-heart failure sheep, there was no statistically significant benefit seen with placement of the RV restraint device for any indices.

**Table 1. The RV Volumes and EF by Cardiac Magnetic Resonance Imaging: Normal Versus RHF (n = 8 Sheep for all Measurements)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>RHF</th>
<th>% Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV EF</td>
<td>0.574 ± 0.04</td>
<td>0.362 ± 0.03</td>
<td>36.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>RV end-diastolic volume</td>
<td>70.8 mL ± 9</td>
<td>82.2 mL ± 7</td>
<td>16.1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<sup>a</sup> Indicates p value < 0.05 versus baseline.

EF = ejection fraction; RHF = right heart failure; RV = right ventricle.

**Fig 3. Magnetic resonance images of right ventricle (RV) dilatation.**

(A) Short axis view of sheep at end-diastole (prior to right coronary artery ligation). Left ventricle (LV) and RV appear normal.

(B) Dilated RV with myocardial scar 8 weeks post infarction.
Optimized RV Restraint Level

Increasing levels of selective RV restraint (ie, wrap tightness) cause greater decreases in RV Ptm and indices of MVO₂. Very high levels of restraint, however, were associated with impaired systemic hemodynamics (ie, tamponade) as seen with decreasing mean arterial pressure in Table 2. This suggests that, as in standard restraint for both ventricles, an optimal restraint level exists for selective RV restraint as well, where the reduction in RV Ptm and RV MVO₂ is maximized while the effect on systemic hemodynamics is minimized.

To analyze this, normalized MAP and normalized RV end-diastolic Ptm were plotted as a function of normalized selective RV restraint levels (normalized to Pmax) (Fig 4). We found that the optimal level of restraint for selective RV QVR (the level which maximizes the reduction in Ptm without causing tamponade) is a normalized restraint value of 0.2 of Pmax for each animal.

Comment

Clinically, ventricular restraint therapy is typically applied to both ventricles in the setting of left heart failure [11-16]. Our previous studies established that adjustable restraint is feasible and promotes reverse LV remodeling more effectively than standard nonadjustable restraint, resulting in improved LVEF and significant reductions in LVEDV [5-8]. Surprisingly, our previous work suggested that without overt RV failure, restraint did not benefit the RV at all [8]. There have been no studies to date of restraint on the RV per se, either in failure or with normal function.

Would restraint benefit the RV in the setting of RV failure? In this study we hypothesized that restraint therapy applied solely to the failing RV would benefit the RV. Previously, several animal models of RHF have been developed, including acute pulmonary artery banding, transvalvular patch placement, and partial balloon occlusion of the pulmonary artery [17-19]. These models are neither physiologic nor chronic with respect to chronic ischemic RHF, typically the most common cause of de novo, intrinsic RHF found clinically.

To address this, we first developed a novel large animal model of chronic ischemic RHF. In a sheep model, we ligated the RCA and allowed RHF to develop over the course of an 8-week interval. We found this approach to be easily reproducible, nonreversible, and chronic, with a low morbidity and mortality. Most importantly, our model successfully mimics the inciting etiology of ischemic RHF as well as its chronicity.

Restraint was then applied to the RV alone (ie, selective RV restraint) to the dilated and failing RV. Similar to our prior studies, we showed that QVR provides benefit (but now to the RV) by decreasing RV Ptm and MVO₂ indices. As restraint levels increased toward Pmax, these key parameters decreased progressively compared with baseline, demonstrating improved acute benefit to the RV. Higher restraint levels also improved RVEF. These findings are consistent with what we have found in studies of
acute restraint on the LV [9], suggesting that in the setting of RV failure, restraint does benefit the RV. If the improved RVEF was simply due to a restrictive effect on end-systolic volume, we would also see a decreased EDV due to the deleterious effects of tamponade, but we did not.

At what level does RV tamponade occur? Is there an optimal level where the benefit is maximized and the adverse effects minimized? By simultaneously plotting normalized MAP and normalized end-diastolic Ptm as a function of normalized restraint levels (normalized to Pmax), we found that the optimal level of restraint for selective RV QVR in chronic RHF is a normalized restraint value of 0.2 of Pmax. This relatively low value is likely related to the mechanical properties of the thin-walled RV, as we hypothesized in our prior work [8]. At this level of restraint, we found the benefit to the RV was maximized while the effect of impaired filling was minimized (Fig 4).

This restraint study is unique in that all prior restraint studies have focused on ischemic or idiopathic left heart failure, either in animal models or humans. We proposed the novel strategy of selective RV restraint for the treatment of chronic, ischemic RHF. One important limitation of this study is that this study was an acute hemodynamic study. We did not evaluate the chronic effect of selective QVR therapy longitudinally on clinical and molecular markers of RV reverse remodeling and contractility; however, this is the object of ongoing studies. In chronic standard restraint, we showed that acute decreases in key LV indices led to LV reverse remodeling and improved LV function [5–7]. It is unclear whether the same would occur in the RV, but we hypothesize that chronic RV selective restraint would lead to chronic RV reverse remodeling. Potential clinical application may include use as an adjunct in cases of open revascularization in patients with RHF.

In summary, we demonstrated that adjustable ventricular restraint applied solely to the dilated, failing RV acutely benefits the RV by decreasing indices of RV MVO2 in a novel sheep model of RV failure. By immediately improving pathologic hemodynamic indices, restraint may have the potential to definitively induce RV reverse remodeling, as has been proven with the LV in LV failure.

This study was supported by NIH R01 HL09862-05 (Chen); NIH F32 HL104923-02 (Kwon); NIH F32 HL105836-01 (Cevasco); and the Paul J. Finnegan Cardiac Surgery Research Fund.

References


DISCUSSION

DR JENNIFER S. LAWTON (St. Louis, MO): Congratulations, Dr. Cevasco and your group, Dr. Chen’s group. You should be congratulated for another great study. I am not that familiar with sheep coronary anatomy, but when you ligated the right coronary artery proximally, did you think that there was any left ventricular effect, so was there any LV myocardium that was supplied? You have MRI images. Could you summarize what you saw in the LV? I know you have reported LV restraint results before, but do you have any LV information, because the LV or the septum could contribute to the right ventricular ejection fraction.

DR CEVASCO: Thank you. That is a great question. We had cardiac MRI available to us. Cardiac MRI, especially with the gadolinium contrast, was a little more informative in terms of truly delineating any scarring or ischemic areas. Using this MRI, we did not see any effect on the LV.

The coronary anatomy of the sheep is more variable than human coronary anatomy. In this study when we did the RCA ligation, the animals that survived the surgery didn’t show any effect on the LV. We did have two intraoperative deaths during the RCA ligation. One hypothesis we had was the animals that died had more septal branches from the right or were right dominant; in other words, had a larger proportion of blood supply to the LV from the RCA. However, given that the animals died, we did not capture it on the MRI. However, for the animals that did survive and underwent MRI, we saw no effect on the LV.

DR LAWTON: And in this study you saw an improvement in ejection fraction with the device, however, end diastolic volume was unchanged. Is that similar to your findings with the LV restraint device?

DR CEVASCO: I’m sorry, what had unchanged?

DR LAWTON: End diastolic volume.

DR CEVASCO: The end diastolic volume of the RV remained unchanged in this study.

In our studies evaluating the left ventricle, we saw that the EDV actually decreased after application of the restraint device.

DR LAWTON: And given the fact that your non ischemic right ventricle did not see an improvement with the restraint device, how does that affect your ability to have some sort of clinical use for this device in the future?

DR CEVASCO: In this study, we used an ischemic model to develop right heart failure, as opposed to something like a pulmonary hypertension model. Given that we saw an improved RV ejection fraction with use of the restraint device, one clinical use of this device would be in a patient or a population with ischemic right heart failure. There are, of course, different etiologies for right heart failure, ischemic failure being one of them, and so we thought that this device would at least be appropriate for that population. It would remain to be tested in other populations with different etiologies of heart failure.

DR LAWTON: I was thinking perhaps during the implant of a left ventricular assist device where often we don’t see immediate right heart failure but perhaps right heart dysfunction over time you could perhaps implant this is sort of going way into the future, of course and then inflate it later when there is manifestation of right heart failure.

DR CEVASCO: That is a great idea.

DR LAWTON: Thank you. Nice study.

DR SHAHAB A. AKHTER (Madison, WI): Did you see any significant tricuspid regurgitation during the course of the study and did the restraint actually improve that?

DR CEVASCO: We did not evaluate the degree of tricuspid regurgitation in this experiment. For our ongoing chronic experiments we have intraoperative echo, and we would be able to assess TR in this setting. But it wasn’t something that we looked at with our cardiac MRI or were able to assess during the acute
experiment. I suppose we are able to go back and look at the cardiac MRI and assess for any degree of tricuspid regurgitation before the restraint was applied.

**DR WAYNE L. HOFSTETTER** (Houston, TX): What is the length of time that you have left the restraint in place so far and have there been thoughts about explanting and have there been any long term effects to the RV in remodeling that have been persistent?

**DR CEVASCO:** The experiment that I just described with the restraint device in place is an acute experiment that took place over about an hour. The lab is actually working on a chronic model that includes implanting the restraint device and leaving it in place for up to eight weeks so far, and it has been met with success. It is a difficult reoperation, as one could imagine. But so far the preliminary analyses from the chronic studies up to eight weeks do show an improvement and some reverse remodeling.

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