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/m^2 ± 9 to 82.2 mL/m^2 ± 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.**

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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 (P_{tm}) without any adverse change in effective LV compliance (C_d) [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 P_{tm}, indices of myocardial oxygen consumption (MVO_2), compliance,

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Abbreviations and Acronyms

C_d	=	compliance
cMRI	=	cardiac magnetic resonance imaging
CVP	=	central venous pressure
EDV	=	end diastolic volume
E_{es}	=	end-systolic elastance
EF	=	ejection fraction
ESV	=	end systolic volume
LV	=	left ventricle
MAP	=	mean arterial pressure
MVO_2	=	myocardial oxygen consumption
P_{max}	=	maximum pressure
P_{tm}	=	transmural pressure
PVA	=	pressure-volume area
QVR	=	quantitative ventricular restraint
RCA	=	right coronary artery ligation
RHF	=	right heart failure
RV	=	right ventricle
TTI	=	tension-time index

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-systolic 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.

RV FAILURE MODEL. A novel post infarction model of RHF was created. Ten normal sheep (including the 5 sheep that underwent baseline imaging) were placed under general anesthesia and underwent sterile mini-right thoracotomy through the fourth interspace. The heart was exposed. The RCA proximal to the takeoff of the first branch was identified and ligated with a 4-0 polypropylene suture. The thoracotomy was closed in layers and the right chest was drained with a single thoracostomy tube introduced through a separate stab incision. After thoracostomy tube removal, animals were extubated and recovered. A cMRI was performed in all surviving subjects 8 weeks after infarction to evaluate for RHF. RHF was defined as a RV EF less than 0.40 as assessed by cMRI. By these criteria, RHF developed in 7 out of 8 (87.5%) surviving animals.

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 atrioventricular 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