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Cardiotropin-1 and Myocardial Strain Change Heterogeneously in Cardiomyopathy

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Background. **The pacing model of heart failure produces heterogeneous changes in wall stress and myocyte diameter. The purpose of this study was to measure regional changes in cardiotrophin-1 (CT-1), a cytokine thought to play a role in LV remodeling, and regional changes in LV strain as measured with magnetic resonance imaging.**

Materials and methods. **Dilated cardiomyopathy was induced in nine mongrel dogs over 4 wk by rapid pacing using a right ventricular epicardial lead. Baseline CT-1 was measured from an apical myocardial biopsy, and regional CT-1 was measured from anterior, lateral, inferior, and septal walls after the induction of heart failure and in six control dogs. Tissue tagged images were divided into similar regions and minimal principal strain (MPS), ejection fraction, and ventricular volumes were compared after induction of heart failure.**

Results. **After induction of heart failure, LV ejection fraction and end-diastolic volume differed significantly from baseline ($P < 0.01$ and $P = 0.02$, respectively). Additionally, regional CT-1 and MPS were significantly different ($P < 0.01$ for both). Cardiotrophin-1 increased significantly in the inferior and septal walls (both $P < 0.01$) but not in the anterior or lateral walls (both $P =$ NS). Minimum principal strain decreased significantly in the inferior and septal walls (both $P < 0.01$) but not in the anterior or lateral walls (both $P =$ NS).**

Conclusion. **The pacing model of heart failure produces heterogeneous changes in regional CT-1 and wall motion as measured by MPS. The greatest regional changes are closest to the pacemaker site: the inferior and septal walls. These differences in regional CT-1 may account for previously noted myocyte hypertrophy and preserved ventricular function in these regions.**

Key Words: **cardiomyopathy; natriuretic peptides; magnetic resonance imaging; cardiotrophin-1; heart failure; strain analysis.**

INTRODUCTION

Cardiotrophin-1 (CT-1) is a member of the interleukin-6 family of cytokines that has been associated with cardiomyocyte hypertrophy *in vitro* [1]. Increased gene expression of CT-1 has been demonstrated in atrial and ventricular tissue from dogs paced into dilated cardiomyopathy [2], and in humans with end-stage dilated cardiomyopathy [3]. Ventricular CT-1 gene activation positively correlates with increased left ventricular mass [2] and precedes ventricular B-type natriuretic peptide (BNP) expression in tachycardia-induced dilated cardiomyopathy in dogs [4], suggesting that CT-1 may be an important paracrine/autocrine factor of myocyte hypertrophy associated with dilated cardiomyopathy. To date, little is known concerning regional expression of CT-1 and BNP and their association with regional ventricular function.

The rapid ventricular pacing model of dilated cardiomyopathy in dogs closely resembles human dilated cardiomyopathy with respect to hemodynamic adaptations, neurohumoral changes, and ventricular hypertrophy [5]. Early left ventricular dysfunction progresses to overt congestive failure with increased filling pressures, depressed left ventricular systolic function, left ventricular dilation, and increased plasma BNP levels. Pacing from a single

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site on the right ventricle causes mechanical discoordination resulting in decreased systolic function and increased wall stress [6]. This increased wall stress is heterogeneous and is highest in the late-activated regions (regions remote from pacemaker lead) because of additional preload in early systole and increased afterload in late systole. These changes have been associated with myocardial remodeling [7] and altered regional protein expression. Regional heterogeneity of function in dilated cardiomyopathy has been identified [8–11] and quantified [12] in humans, however, these changes in function have not been demonstrated in the pacing model of dilated cardiomyopathy nor correlated to changes in CT-1 or BNP expression.

We have previously used magnetic resonance imaging (MRI) with myocardial strain analysis to quantitate regional changes in regional left ventricular function after coronary artery bypass grafting [13], and in patients with dilated cardiomyopathy [14]. The goals of this study were to quantitate regional changes in left ventricular function in dogs with dilated cardiomyopathy using myocardial strains and to identify changes in tissue expression of CT-1 and BNP associated with these changes in function.

MATERIALS AND METHODS

Overview

After approval by our institution's animal care and use committee, nine mongrel dogs of either gender underwent baseline cardiac MRI for regional strain, regional wall thickness, and global cardiac volume measurements. The dogs then had a pulmonary artery catheter placed for thermodilution hemodynamic measurements, a blood draw for baseline plasma BNP levels, and an epicardial right ventricular pacemaker lead was implanted. After 1 wk of recovery, the dogs were rapidly paced into a dilated cardiomyopathy. Following the pacing protocol, the dogs underwent repeat MRI measurements, thermodilution hemodynamics, and plasma BNP measurements. The dogs were then sacrificed and tissue levels of CT-1 and BNP were measured from the anterior, lateral, posterior, and septal walls. Additionally, six control dogs were sacrificed for normal heart tissue.

Baseline MRI Acquisition

After induction of anesthesia, imaging was performed on a 1.5 tesla MRI scanner (Signa Excite; GE Medical Systems, Milwaukee, WI). Short axis images were acquired first with tags for myocardial strain measurement and then without tags for wall thickness and cardiac volume measurement. For both acquisitions, the pulse sequence was a 2D gradient echo sequence that was electrocardiographically (ECG) gated and performed during breath holds. Except for the presence of tags, the scan prescription was identical between the two acquisitions and included the following parameters: slice thickness = 7 mm, gap = 0 mm, field of view = 360 mm, matrix = 256 × 128, flip angle = 20°, number of excitations = 1. TE was selected as minimum, which resulted in TEs that ranged between 1.4 and 5.2 ms (mean = 5.0). TR was not manipulatable by the operators but ranged between 8.7 and 8.8 ms. The number of cardiac phases acquired per slice was 20. For tagged imaging, spatial modulation of magnetization (SPAMM) was used to create an orthogonal grid pattern of presaturation in the short axis.

Invasive Hemodynamics

Hemodynamics were measured using the thermodilution technique via a pulmonary artery catheter. The following measurements were acquired: systolic blood pressure (SBP), central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), cardiac index (CI), and systemic vascular resistance index (SVRI). Measurements were performed under general anesthesia prior to surgical manipulation.

Pacemaker Placement

Anesthesia was induced by ketamine/diazepam (13 mg/0.65 mg/kg) and maintained by 1% inhaled isoflurane. Via a right thoracotomy, an epicardial pacing lead (Medtronic, Minneapolis, MN) was sutured to the mid-right ventricular free wall and the pacemaker generator (model series 700 or 900; Medtronic, Minneapolis, MN) was tunneled subcutaneously. A low sodium diet (Hill's prescription i/d diet; Hill's Pet Nutrition Inc., Topeka, KS) was begun 3 d prior to pacemaker implantation and maintained throughout the protocol. Butorphal (0.3 mg/kg) was used for postoperative pain control and cefazolin (25 mg/kg) was given for prophylactic antibiosis.

Pacing Model of Dilated Cardiomyopathy

After a recovery period of 1 wk, rapid pacing was begun at 180 beats per min for 14 d. Pacing was increased to 200 beats per min for 7 d and finally to 240 beats per min for 7 d. Pacing rate was confirmed by palpation and electrocardiogram prior to each intervention.

Follow-Up Studies

After induction of cardiomyopathy, the pacemaker was turned off and the generator was removed under anesthesia. Within 15 h of turning off the pacemaker, repeat studies were performed. The dogs underwent repeat MRI, thermodilution hemodynamic measurement, and blood draw. Each dog was then euthanized with Sleepaway (sodium pentobarbital 1 mL/5 lb; Fort Dodge Animal Health Inc., Fort Dodge, IA), the heart rapidly excised, and placed in an ice slurry. The left ventricle was divided into septal, anterior, lateral, and posterior regions, and snap frozen in liquid nitrogen. Six dogs that had undergone noncardiac vascular procedures were euthanized in a similar fashion, the left ventricle divided into four regions, and the tissue was snap frozen in liquid nitrogen for use as control myocardial tissue.

MRI Regional Strain Analysis

Using the tagged MRI images, strains were calculated for the anterior, lateral, posterior, and septal walls. To define the four walls, a point was placed on the anteroseptal right ventricular insertion onto the left ventricle. Using that insertion the left ventricle was divided into four equal segments.

Anterior wall strain was the average of the anterior wall strain of three slices— apical, mid-ventricular, and basal. The strain for the lateral, posterior, and septal walls were each calculated in the same way. The apical slice was defined by the origins of the papillary muscles. The mid-ventricular slice was defined first as the image halfway between the most apical image with myocardium and the image at the mitral valve annulus. The basal slice defined by the tips of the papillary muscles. Images at baseline and after induction of dilated cardiomyopathy were matched by visual side-by-side comparison (Fig. 1).

Strain is a measure of deformation. Because tag lines form grids, they define points whose displacements can be measured and from which strains can be calculated. To track the displacement of the points, tag lines were located on successive images from diastole to systole. In this study, the initial tag lines were constructed from the end-diastolic