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Left Atrial Reverse Remodeling in Dogs with Moderate and Advanced Heart Failure Treated with A Passive Mechanical Containment Device: An Echocardiographic Study

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Abstract

Background—Assessment of global LV remodeling is important in evaluating the efficacy of pharmacologic and device therapies for the treatment of chronic heart failure (HF). The effects of pharmacologic or device therapies on global left atrial (LA) remodeling in HF, while also important, are not often examined. We showed that long-term therapy with the Acorn Cardiac Support Device (CSD), a passive mechanical ventricular containment device, prevents and/or reverses LV remodeling in dogs with HF. This study examined the effects of the CSD on global LA remodeling in dogs with moderate and advanced HF.

Methods and Results—Studies were performed in 24 dogs with coronary microembolization-induced HF. Of these, 12 had moderate HF (ejection fraction, EF 30% to 40%) and 12 advanced HF (EF ≤25%). In each group, the CSD was implanted in 6 dogs and the other 6 served as controls. Dogs were followed for 3 months in the moderate group and 6 months in the advanced HF group. LA maximal volume (LAVmax), LA volume at the onset of the p-wave (LAVp), LA minimal volume (LAVmin), LA active emptying volume (LAAEV) and LA active emptying fraction (LAAEF) were measured from 2-dimensional echocardiograms obtained prior to CSD implantation and at the end of the treatment period. Treatment effect (Δ) comparisons between CSD-treated dogs and controls showed that CSD therapy significantly decreased LA volumes (ΔLAVmax: 3.33 ± 0.70 vs. −2.87 ±1.31 ml, p=0.002; 7.77 ± 1.76 vs. −0.37 ± 0.87 ml, p=0.002) and improved LA function (ΔLAAEF: −6.00 ± 1.53 vs. 1.85 ± 1.32 %, p=0.003; −2.39 ± 1.10 vs. 3.13 ± 1.66 %, p=0.02) in the moderate HF and advanced HF groups respectively.

Conclusions—Progressive LA enlargement and LA functional deterioration occurs in untreated dogs with HF. Monotherapy with the CSD prevents LA enlargement and improves LA mechanical function in dogs with moderate and advanced HF indicating prevention and/or reversal of adverse LA remodeling.

Keywords

Atrium; Echocardiography; Heart failure; Heart-assist device

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Introduction

Left ventricular (LV) remodeling is a key component leading to progressive worsening of all forms of heart failure (HF) (1). Left ventricular remodeling is characterized by structural reorganization of both cardiomyocytes and extracellular matrix (ECM), a process that ultimately translates into global LV geometrical and functional modifications (1,2). Bi-atrial or left atrial (LA) chamber enlargement is a common echocardiographic finding in patients with HF and a well-known risk factor for the development of atrial fibrillation (AF) in this patient population (3-5). Analyses from Studies of Left Ventricular Dysfunction (SOLVD) trial and the Cardiovascular Health Study (CHS) pointed out the importance of increased LA size as an independent predictor of adverse cardiovascular events in HF patients (6,7).

The molecular and structural bases for atrial remodeling differ qualitatively and quantitatively from that of LV remodeling (8) but ultimately lead to a significant LA dilation and LA functional deterioration (9-10). The LA has a pivotal role in modulating LV filling through three phases: a reservoir phase, a conduit phase, and an active contraction phase (atrial booster) (11), and in the course of HF all these 3 phases are impaired. Numerous pharmacological interventions have been reported to affect LA performance both in experimental animal models and in patients with HF. Vasodilator therapy with nitroprusside for instance was shown to acutely improve LA function (12,13), while the benefit of positive inotropic agents, if any, remains controversial (12-14). Studies have also shown that short-term digoxin and long-term therapy with β-blockers increase LA contractile performance and atrial contribution to LV filling (15,16).

Device-based therapy is on the rise as an alternative or adjunctive therapy for treating HF (17). The role of such devices in the prevention and/or reversal of LA remodeling has not been studied. The Acorn Cardiac Support Device (CSD), a passive mechanical ventricular containment device, has been demonstrated to effectively prevent LV dilation and to improve LV ejection fraction (EF) in dogs with HF (18), but its effect on LA size and function is not known. In the present study we examined the effects of the CSD on LA size and function in a dog model of intracoronary microembolization-induced HF.

Methods

Experimental Model

The canine model of chronic HF used in this study was previously described in detail (19). Chronic LV dysfunction was produced by multiple sequential coronary microembolizations with polystyrene Latex microspheres (70-102 μm in diameter), which result in loss of viable myocardium. The model manifests many of the hemodynamic and neurohormonal sequelae of HF observed in humans including marked and progressive depression of LV systolic and diastolic function, reduced cardiac output, and increased LV filling pressures. In the present study, 24 healthy mongrel dogs underwent serial coronary microembolizations to produce HF. Embolizations were performed 1 to 3 weeks apart and were discontinued in 12 dogs when LV EF was between 30 and 40% (Moderate HF group). In this group, control dogs weighed 23.3 kg (range 21.2 to 27.0 kg) and HF dogs weighed 24.1 kg (range 21.6 to 26.5 kg). In the remaining 12 dogs the embolizations were discontinued when EF was ≤25% (Advanced HF group). In this group, control dogs weighed 25.3 kg (range 22.2 to 30.0 kg) and HF dogs weighed 27.5 kg (range 20.2 to 29.0 kg). All the procedures were performed during cardiac catheterization under general anesthesia and sterile conditions. The anesthesia regimen consisted of a combination of intravenous administration of oxymorphone (0.22 mg/kg), diazepam (0.17 mg/kg), and sodium pentobarbital (150-250 mg to effect).

Study Protocol

Dogs underwent a left and right heart catheterization and a complete 2-dimensional (2-D) and Doppler echocardiogram at baseline, before any coronary microembolization and again 2 weeks after the last embolization (pre-treatment). Six dogs from the Moderate HF group and 6 dogs from the Advanced HF group were then surgically implanted with the CSD as previously described (18). The remaining 6 dogs in both groups did not undergo surgery and served as concurrent controls. All CSD-implanted dogs and controls were followed up for 3 months in the moderate HF group and for 6 months in the advanced HF group without receiving any concomitant cardioactive drug. At the end of the follow-up period, a final left and right cardiac catheterization (post-treatment) and a complete echocardiographic and Doppler study were performed. The study was approved by the Henry Ford Health System Institutional Animal Care and Use Committee and conformed to the "Position of the American Heart Association on Research Animal Use" (20).

Ventriculographic and Echocardiographic Measurements

Single-plane left ventriculograms were obtained during left heart catheterization with the dog placed on its right side. Ventriculograms were recorded on 35 mm cine film at 30 frames per second during the injection of 20 ml of contrast material (Reno-M-60, Squibb). Correction for image magnification was made with a radiopaque calibrated grid placed at the level of the LV. LV end-systolic and end-diastolic volumes (ESV and EDV, respectively) were calculated from LV silhouettes using the area-length method. LV EF was calculated as the difference between end-diastolic and end-systolic volumes divided by end-diastolic volume times 100 (19).

Echocardiograms were performed using a model 77030A ultrasound system (Hewlett-Packard, Sonos 1000; Andover MA) with a 3.5 MHz transducer and recorded on a Panasonic 6300 VHS recorder for subsequent off-line analysis. Measurements were made under general anesthesia with the dog placed in the right lateral decubitus position. Off-line analysis was carried out by one reader blinded to treatment regimen. All VHS echocardiographic tapes used in the off-line analysis were labeled by dog number only. The CSD is not echogenic and it cannot be detected or appreciated by echocardiography or by fluoroscopy. The LA antero-posterior diameter (D1) was obtained from the parasternal long-axis view, while the longitudinal (D2) and the transverse (D3) diameters were obtained from the apical four-chamber view. All the diameters were determined at each of the following time-points of the cardiac cycles: a) one frame after mitral valve opening, b) at time of onset of the p-wave, and c) one frame prior to mitral valve closure. LA volumes were calculated using the ellipsoidal formula: $LAV = (D1 * D2 * D3) * \pi/6$, as previously described (21). To determine LA dimensions, the LA maximal volume at mitral valve opening (LAVmax), the LA minimal volume at mitral valve closure (LAVmin), and the LA volume at the onset of atrial systole (corresponding to the onset of the p-wave) (LAVp) were calculated (14). LA mechanical function was evaluated by determining the LA active emptying volume (LAAEV)=[LAVp-LAVmin], and the LA active emptying fraction (LAAEF)={[(LAVp-LAVmin)/LAVp] * 100} as previously described (14). Each of the above parameters were measured in triplicate and the average of the 3 measurements was reported.

Statistical Analysis

Angiographic and echocardiographic measurements between Control and CSD-treated dogs in both study groups at baseline were compared using a *t*-statistic for two means with a $p<0.05$ considered significant. Within group comparisons of baseline, pre- and post-treatment measures were made using repeated measures of analysis of variance (ANOVA) with alpha set at 0.05. If significance was attained, pairwise comparisons were performed using the Student-Newman-Keuls test. For this test, a probability value ≤ 0.05 was considered significant. To determine treatment efficacy or treatment effect, the change (Δ) in each measure from pre- to post-treatment was calculated for each of the study arms. For this comparison, a *t*-statistic

for two means was used with $p<0.05$ considered significant. All the data are reported as the mean ± SEM.

Results

All dogs entered into the study had baseline angiographic and echocardiographic measures within the range of normality for mongrel dogs in our laboratory. Baseline echocardiographic data for both study groups are shown in Table 1. There were no significant differences in any of the echocardiographic measures obtained at baseline between Control dogs and dogs subsequently treated with the CSD. Similarly, there were no significant differences in echocardiographic measure at pre-treatment between Control dogs and dogs subsequently implanted with a CSD. This was true for both the moderate HF study group as well as the advanced HF study group (Table 2 and 3).

Progression of LA Remodeling and Dysfunction in Control Dogs

The echocardiographic findings at pre- and post-treatment in Control dogs in the moderate and advanced HF groups are shown in Table 2. In the moderate HF group, LAVmax increased significantly during the 3-month follow-up period. This finding was accompanied by a parallel increase in LAVp and LAVmin. This significant dilation of the LA was associated with a significant decrease in both LAAEV and LAAEF. In the advanced HF group, LAVmax also increased significantly over the course of the 6-month follow-up period, and was associated with significant increase of both LAVp and LAVmin. A trend suggestive of a further deterioration of LA contractile performance as determined by decreased LAAEV and LAAEF was present but the decrease did not reach statistical significance.

Effects of CSD Therapy

The echocardiographic findings at pre- and post-treatment period for CSD implanted moderate and advanced HF dogs are shown in Table 3. In dogs with moderate HF treated with the CSD, LAVmax decreased significantly after 3 months of therapy, and this finding was accompanied by a significant decrease of both LAVp and LAVmin. Unlike observation made in Control dogs, CSD therapy in this group of moderate HF dogs, was associated with no reduction of LAAEV and LAAEF (Table 3). In dogs with advanced HF treated with the CSD, LAVmax, LAVp and LAVmin were essential unchanged at post-treatment compared to pre-treatment. There was a modest increase in LAAEV and LAAEF but neither reached statistical significance (Table 3).

Treatment Effect

The comparisons between Control dogs and CSD-treated dogs of the change (Δ) measured as the difference between pre-treatment and post-treatment in echocardiographic measures are shown in Table 4. In dogs with moderate HF, treatment with the CSD resulted in a significantly smaller LAVmax, LAVp and LAVmin. Furthermore treatment with the CSD preserved LAAEV and significantly increased LAAEF (Table 4). In dogs with advanced HF, treatment with the CSD also resulted in a significantly smaller LAVmax, and smaller but only borderline significant LAVp and LAVmin. Treatment with the CSD in this group of dogs with advanced HF resulted in a significant increase of both LAAEV and LAAEF (Table 4).

Discussion

LA Reverse Remodeling with CSD Therapy

The present study demonstrates that implantation of the Acorn CSD is effective in preventing LA enlargement and in improving LA mechanical performance in dogs with moderate and

advanced HF. This observation is particularly reassuring because the CSD operates by containing the ventricles and preventing progressive LV dilation with no readily apparent theoretical evidence that such a device would favorably impact progressive LA remodeling. The beneficial effects of the CSD on LA remodeling was particularly evident in the moderate HF group which manifested true LA reverse remodeling with a reduction in all measures of LA volumes and improved LA contractile performance. Nonetheless, even in dogs with advanced HF, chronic therapy with the CSD prevented progressive LA enlargement leading to a functional improvement. These data, when viewed in concert suggests that LA intrinsic contractile dysfunction in the setting of HF is a potentially reversible process regardless of the severity of the disease. The possibility of partially recovering the atrial booster function, exhibited in CSD dogs from the advanced HF group, may be of critical importance in the clinical setting of advanced HF (New York Heart Association class III and IV) since it has been demonstrated that the loss of LA contraction reduces cardiac output by 15-20% in this patient population (22).

Possible Mechanisms of LA Reverse Remodeling with CSD Therapy

The exact mechanisms by which a CSD type HF therapy elicits improved LA function and prevention of LA remodeling is not fully understood. One possibility is that the benefits of the CSD on the left atrium are a consequence of and, possibly secondary to, improved LV hemodynamics. Previous reports from our laboratory and others demonstrated that the Acorn CSD prevents progressive LV dilation and improves LV EF in animals with HF (18,23-27). These benefits are obtained through the prevention of progressive LV dilation and prevention of progressive LV chamber sphericity; the latter potentially responsible for the observed attenuation of functional mitral regurgitation (18,23-27). The CSD has also been shown to preserve LV diastolic function as evidenced by prevention of progressive LV end-diastolic pressures rise, reduced LV end-diastolic wall stiffness and wall stress, decreased deceleration time and preservation of PE/PA ratio (18,23-27). CSD-mediated improvement in LV hemodynamics can indirectly lead to an improvement in LA hemodynamics resulting in decreased LA pressure and wall tension, thus limiting the stretch-induced neurohormones release with a resulting increase of collagen synthesis and deposition in the interstitial compartment (28,29); the latter promoting further adverse LA adverse remodeling. These favorable hemodynamic and neurohumoral conditions associated with chronic CSD therapy can themselves contribute to the maintenance of a favorable workload condition that limits or retards LA adverse remodeling.

LA Reverse Remodeling with Pharmacologic Therapy

Numerous pharmacological agents have been reported to improve LA dysfunction in HF (12-16) or in experimental condition of elevated LV filling pressure (30). In dogs with moderate HF (EF 30-40%) long-term administration of metoprolol was shown to significantly improve LA contribution to LV filling through the ability of β-blockers to reduce LA workload with decreased LV end-diastolic pressure, wall stress and stiffness (16). Short-term digoxin therapy was shown to positively affect LA function with concomitant acute or sub-acute LA volume reduction in a cohort of patients with post-ischemic HF (EF∼35%) (15). Vasodilators and inotropic agents are often used as an adjunct to optimal medical therapy in the treatment of severe HF. Available data in the literature indicate that nitroprusside, for instance, significantly restores atrial pump function by reducing LA workload both in experimental animal models and in patients with congestive HF (12,13). In patients with idiopathic dilated cardiomyopathy and NYHA class III, 10 minutes of dobutamine infusion induced a significant LA volume reduction and increased LA pump function (14). Other studies, however, failed to show such a benefit with dobutamine (12). The current study is the first to demonstrate that a chronic passive mechanical device such as the CSD that primarily targets remodeling of the cardiac ventricles can also lead to considerable left atrial improvement of both global function and

global structure. The extent to which the benefit of chronic CSD therapy on LA remodeling can translate to improved clinical outcome in patients with heart failure remains to be elucidated.

Study Limitations

A limitation of the present study is its retrospective nature. The 3 months moderate HF study and the 6 months advanced HF study were not conducted concurrently. The decision to extend the advanced HF study to 6 months was made at the time the study was conducted to gain more insight into the long-term benefits of CSD therapy on LV function and remodeling. The study would have clearly benefited further from having serial echocardiograms. Histomorphometric and molecular analyses could not be carried out as LA tissue was not collected at the time of the original studies. Therefore, a comprehensive examination of the mechanisms through which CSD therapy elicits improvement in LA function and remodeling is not possible. Previous observations with pharmacological interventions have partially documented the molecular and structural basis of LA reverse remodeling. Atrial fibrosis has been implicated in LA chamber stiffness (31) and decreasing LA contractility (32). Administration of the ACE-inhibitor enalapril resulted in a significant reduction of LA fibrosis and improvement of fractional shortening without worsening of LA dimension (32). Similar inhibitory effect on LA fibrosis has also been reported with the aldosterone receptor antagonist spironolactone alone or in combination with ACE inhibitors and β-blockers (33). Thus attenuating LA fibrosis can improve LA compliance and may also favorably modify LA electrophysiological properties (32,33) potentially leading to the development of a morphostructural substrate that is less vulnerable to the development of AF or other atrial tachyarrhythmias. While the present study clearly identifies CSD therapy as favorable toward LA reverse remodeling, additional studies are needed to complement these global findings with observations at the cellular and molecular levels.

The use of the ellipsoidal formula potentially leads to an underestimation of LA volumes because it does not account for the LA corners (34); this might be particularly true in extremely dilated atria as the chamber remodeling process follows an asymmetric trend. However the use of the formula applied in our paper has been validated in large echocardiographic series (7, 35) and has been shown to provide data that correlate closely to those obtained with the biplane Simpson's method and the 4-chamber area-length method (36,37). Determination of LAAEV and LAAEF is commonly used in clinical practice for the evaluation of LA mechanical function as these parameters reflect the intrinsic contractile property of the chamber (14,38). Additional useful information would have been attained if these measures were integrated with data derived from Doppler analysis of transmitral and pulmonary vein flow (38). Both these parameters allow for an accurate assessment of LV diastolic function and pressures as well as right ventricular function and pulmonary vasculature compliance, thus providing further insight into the hemodynamic framework of the LA (38,39).

Conclusions

The results of the present study indicate chronic CSD therapy, in addition to improving LV function and preventing progressive LV remodeling, also affords considerable benefits on LA function and remodeling. The benefits of CSD therapy on LA function and chamber remodeling appears to be present regardless of the severity of LV dysfunction and, hence severity of HF. The extent to which such benefits of CSD therapy on LA remodeling can lead to reduced risk of adverse cardiovascular events and occurrence of AF in patients with HF remains uncertain.

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Table 1

Ventriculographic and Echocardiographic Measures at Baseline in Dogs with Moderate and Advanced Heart Failure .

	Moderate HF (n=12)			Advanced HF (n=12)		
	Control (n=6)	CSD (n=6)	P-value	Control (n=6)	CSD (n=6)	P-value
LV EF (%)	55±1	53±2	0.37	48±1	50±1	0.18
LAVmax (ml)	15.20±1.35	16.20±1.10	0.58	18.90±2.2	21.10±2.20	0.49
LAVp (ml)	11.10±0.73	12.10±1.02	0.44	13.00±2.00	15.33±1.59	0.38
LAVmin (ml)	8.90±0.65	9.20±0.73	0.77	10.25±1.63	12.2±1.35	0.38
LAAEV (ml)	2.36±0.16	2.90±0.33	0.17	2.75±0.37	3.15±0.51	0.54
LAAEF (%)	21.60±1.76	23.70±1.02	0.32	21.50±1.24	20.75±1.76	0.73

HF = heart failure; LV = left ventricular; EF = ejection fraction; LAVmax = left atrial maximal volume; LAVp = left atrial volume at the onset of the p wave; LAVmin = left atrial minimal volume; LAAEV = left atrial active emptying volume; LAAEF = left atrial active emptying fraction.

Table 2

Ventriculographic and Echocardiographic Measures Obtained Before (Pre-treatment) and at the End of Follow-Up (Post-treatment) in Control dogs.

	Moderate HF (n=6)		Advanced HF (n=6)	
	Pre-treatment	**Post-treatment**	**Pre-treatment**	**Post-treatment**
LV EF (%)	36±1	28±2*	24±1	19±1*
LAVmax (ml)	23.12±1.48	26.42±1.47*	27.63±2.26	35.4±3.12*
LAVp (ml)	15.57±0.65	18±0.91*	18.46±1.55	25.87±4.32*
LAVmin (ml)	13.33±0.65	16.5±0.92*	16.68±1.46	24.2±4.56*
LAAEV (ml)	2.23±0.22	1.5±0.09*	1.78±0.17	1.67±0.21
LAAEF (%)	14.40±1.33	8.4±0.68*	9.76±0.82	7.37±1.38

Abbreviations as in Table 1.

* $p<0.05$ vs. Pre-treatment.

Table 3

Ventriculographic and Echocardiographic Measures Obtained Just Prior to CSD Implantation (Pre-treatment) and at the End of Follow-Up (Post-treatment) in CSD-Treated Dogs.

	Moderate HF (n=6)		Advanced HF (n=6)	
	Pre-treatment	**Post-treatment**	**Pre-treatment**	**Post-treatment**
LV EF (%)	34±1	42±1*	25±1	27±1
LAVmax (ml)	22.37±1.44	19.50±0.74*	28.42±1.58	28.05±1.63
LAVp (ml)	16.47±0.99	13.75±1.02*	21.10±1.4	20.35±0.79
LAVmin (ml)	14.35±1.02	11.65±0.94*	19.00±1.20	17.67±0.82
LAAEV (ml)	2.12±0.19	2.10±0.11	2.12±0.2	2.70±0.24
LAAEF (%)	13.17±1.38	15.02±0.8	9.98±0.77	13.12±1.28

Abbreviations as in Table 1.

* $p<0.05$ vs. Pre-treatment.

Table 4

Comparisons of the Change (Δ) Between Control Dogs and CSD-Treated Dogs of Ventriculographic and Echocardiographic Measures.

	Moderate HF (n=12)			Advanced HF (n=12)		
	Control	CSD	P-value	Control	CSD	P-value
LV EF (%)	−8±2.24	8±1.41	<0.001	−5±1.4	2±1.41	0.006
LAVmax (ml)	3.33±0.7	−2.87±1.31	0.002	7.77±1.76	−0.37±0.87	0.002
LAVp (ml)	2.43±0.41	−2.72±0.76	<0.001	7.41±4.03	−0.75±1.38	0.08
LAVmin (ml)	3.17±0.42	−2.70±0.72	<0.001	7.52±4.19	−1.48±1.34	0.07
LAAEV (ml)	−0.73±0.28	−0.02±0.1	0.06	−0.11±0.16	0.58±0.29	0.006
LAAEF (%)	−6.00±1.53	1.85±1.32	0.003	−2.39±1.1	3.13±1.66	0.02

Abbreviations as in Table 1.