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PRECLINICAL STUDY

Therapy With Cardiac Contractility Modulation Electrical Signals Improves Left Ventricular Function and Remodeling in Dogs With Chronic Heart Failure

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Objectives This study examined the effects of long-term delivery of cardiac contractility modulation (CCM) electric signals on left ventricular (LV) function and global, cellular, and molecular remodeling in dogs with chronic heart failure (HF).

Background Acute studies in dogs with experimentally induced HF showed that CCM signals applied to the failing myocardium during the absolute refractory period improved LV function without increasing myocardial oxygen consumption.

Methods In one study, dogs with intracoronary microembolization-induced HF were randomized to 3 months of active CCM monotherapy or to a sham-operated control group. In another study, 19 HF dogs were randomized to 3 months chronic monotherapy with extended release metoprolol succinate (MET-ER), MET-ER with CCM, or no therapy at all (control group).

Results In CCM-only treated dogs, LV ejection fraction (EF) increased (27 ± 1% vs. 33 ± 1%, $p < 0.0001$) compared with a decrease in sham-operated control animals (27 ± 1% vs. 23 ± 1%, $p < 0.001$). The increase in EF seen with CCM-treated dogs was accompanied by reduced LV volumes, improved myocardial structure, reversal of the maladaptive fetal gene program, and an improvement in sarcoplasmic reticulum calcium cycling proteins. Dogs treated with a combination of MET-ER and CCM showed a greater increase in LV EF and a greater reversal of LV global, structural, and biochemical remodeling compared with dogs treated with MET-ER alone.

Conclusions In dogs with HF, long-term CCM therapy improves LV systolic function. The improvements are additive to those seen with beta-blockers. These findings are further strengthened by the concomitant benefits of CCM therapy on LV global, cellular, and biochemical remodeling. (J Am Coll Cardiol 2007;49:2120–8) © 2007 by the American College of Cardiology Foundation

Despite improvements in pharmacologic therapy for chronic heart failure (HF) (1–3), a large number of patients with New York Heart Association functional class III and IV are refractory to optimal standard medical therapy. The need for further therapeutic interventions in this patient population has given rise to a host of device-based therapies such as cardiac resynchronization therapy. Cardiac resynchronization therapy has been shown to improve left ventricular (LV) systolic function in a subset of patients with dyssynchrony of myocardial contraction (4–7). Cardiac contractility modulation (CCM) electrical signals delivered to the failing myocardium during the absolute refractory period is another device-based therapy targeting this advanced HF population (8). In dogs with chronic HF, CCM signals applied acutely via leads sutured directly to the LV epicardium (9) or longer term via leads placed retrograde into the coronary sinus and positioned in the anterior coronary vein (10) resulted in improved LV systolic function (9,10). Preliminary clinical studies of CCM signals delivered to the myocardium of patients with chronic HF suggest that CCM therapy is safe and can also improve exercise tolerance and quality of life (11,12). In dogs with HF, classical positive inotropic agents such as dobutamine also improve LV systolic function but at a cost that the failing heart can ill afford, namely, an increase in myocardial oxygen con-

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sumption (MVO_2) (13). In contrast, acute delivery (2 h) of CCM therapy in dogs with chronic HF was associated with improved LV function and with no increase in MVO_2 (8). The purpose of this study was to determine: 1) whether long-term CCM monotherapy improves LV systolic function when used alone and in combination with a beta-blocker; 2) whether CCM therapy elicits improvement in LV remodeling both globally and at the cellular and molecular levels; and 3) potential mechanisms that underlie the improvement in LV function seen with CCM therapy.

Methods

Animal model. The dog model of chronic HF used in the present study was previously described in detail (14–16). In this study, healthy mongrel dogs weighing between 20 kg and 30 kg underwent coronary microembolizations to produce HF. Microembolizations were performed during cardiac catheterization under general anesthesia and sterile conditions. Animals were induced with intravenous oxymorphone hydrochloride (0.22 mg/kg) and diazepam (0.17 mg/kg), and a plane of anesthesia was maintained with 1% to 2% isoflurane. The study was approved by Henry Ford Health System Institutional Animal Care and Use Committee.

Implantation of the CCM system. Two weeks after the target LV ejection fraction (EF) was reached, dogs were anesthetized, intubated, and ventilated with room air. The right external jugular vein was surgically exposed and used to position the CCM leads. Two standard active fixation leads were advanced into the right ventricle, positioned on the anterior and posterior septal grooves, and used to sense ventricular activity and deliver CCM electrical signals. A third lead was positioned in the right atrium for p-wave sensing (Fig. 1). The leads were connected to a CCM signal generator (OPTIMIZER II, Impulse Dynamics USA, Inc., Orangeburg, New York) implanted in a subcutaneous pocket created on the right side of the neck. As observed in clinical studies to date (8), there was no induction of ventricular or atrial ectopic beats, atrial fibrillation, or intercostal stimulation. Diaphragmatic stimulation was also avoided by testing signal application during the implant and moving the leads if a problem was observed. Studies were initiated 2 weeks after CCM system implantation to allow leads to stabilize in place.

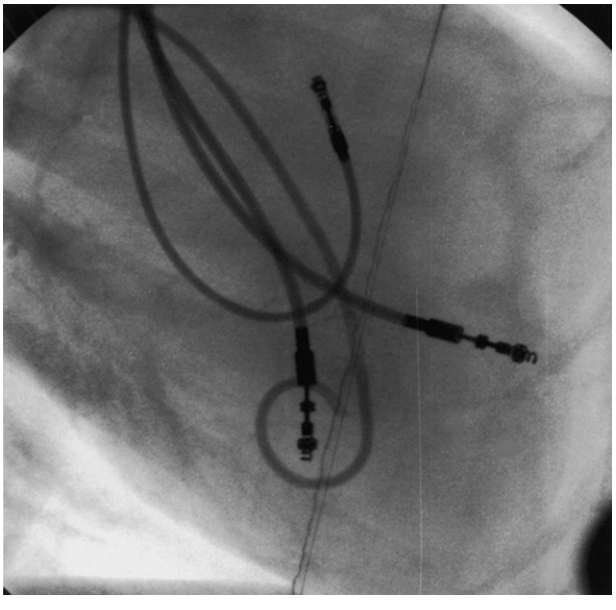

Figure 1 Right Anterior Oblique Fluoroscopic Image of Leads Placement During CCM System Implantation

CCM = cardiac contractility modulation.

Chronic study protocol—monotherapy with CCM. Fourteen dogs were embolized to achieve a target LV EF, determined angiographically, of <30%. Two weeks after device implantation, dogs underwent a pretreatment left and right heart catheterization and were then randomized to 3 months of active treatment group (n = 7) or to a sham-operated control group (n = 7). In the active group, CCM therapy was administered for 5 h/day based on a duty cycle of 1 h ON and 3 h and 48 min OFF for 3 months. During ON periods, CCM signals were delivered on every beat after a delay from the detection of electrical activity at one of the right ventricular leads. As detailed previously (12), the signals consisted of 2 biphasic pulses having a total pulse width of 20.56 ms (10.28 ms/pulse) with an amplitude of ±7.73 V. Control dogs did not receive any therapy. At the end of 3 months of therapy or follow-up, all hemodynamic measurements were repeated. Finally, while under general anesthesia, the chest was opened and the heart rapidly harvested and tissue prepared for histological and biochemical evaluation. Tissue from 6 normal dogs were obtained and prepared in the same manner for comparisons. All tissue was stored at −70°C until needed.

Abbreviations and Acronyms

ANP = atrial natriuretic peptide
AR = adrenergic receptor
BNP = brain natriuretic peptide
CCM = cardiac contractility modulation
CD = capillary density
CSQ = calsequestrin
EDV = left ventricular end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
GAPDH = glyceraldehyde-3-phosphate dehydrogenase
HF = heart failure
LV = left ventricular
MCSA = myocyte cross-sectional area
MET-ER = metoprolol succinate-extended release
MHC = α-myosin heavy chain
MVO_2 = myocardial oxygen consumption
ODD = oxygen diffusion distance
PLB = phospholamban
P-PLB = phosphorylated phospholamban
RyR = ryanodine receptor
SERCA-2a = sarcoplasmic reticulum calcium ATPase
SR = sarcoplasmic reticulum
VFIF = volume fraction of interstitial fibrosis
VFRF = volume fraction of replacement fibrosis