Treating Heart Failure with Cardiac Contractility Modulation Electrical Signals

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Major advances have been made over the past two decades in the pharmacologic treatment of chronic heart failure (HF). Angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists have had a substantial impact on reducing mortality and morbidity in patients with HF and low left ventricular ejection fraction. These treatments delayed the progression toward advanced intractable HF but did not arrest progressive worsening of the disease. Patients on optimal medical therapy continued to deteriorate, albeit at a much slower pace, ultimately requiring further intervention. This gave rise to a host of device-based therapies that emerged in recent years to address this unmet need. Device therapies such as cardiac resynchronization, the CorCap™ cardiac support device (Acorn Cardiovascular, Inc., St. Paul, MN), and the OPTIMIZER™ System (Impulse Dynamics USA, Inc., Orangeburg, NY) are a few examples. This review addresses the progress made to date in the development and implementation of cardiac contractility modulation (CCM) as a device-based therapy for the treatment of patients with advanced HF. Treatment of patients with HF using CCM electrical signals is at present an investigational form of therapy.

Introduction

Despite major advances over the past two decades in the pharmacologic treatment of patients with chronic heart failure (HF) and low ejection fraction (EF), HF remains one of the leading causes of morbidity and mortality in Western countries. Pharmacologic therapy with angiotensin-converting enzyme inhibitors [1], β-adrenergic receptor blockers, [2] and more recently aldosterone antagonists [3] has substantially reduced mortality and morbidity in patients with HF. Despite having slowed down the progression of the disease, therapy has not arrested it. As a result, a large number of patients with HF who are on optimal medical therapy survive with a markedly limited quality of life, manifested by worsening symptoms of HF. Ultimately these patients succumb to the disease. The need for further therapeutic interventions in this patient population has given rise to a host of device-based therapies such cardiac resynchronization therapy (CRT) [4], left ventricular (LV) containment devices such as the CorCap™ cardiac support device (Acorn Cardiovascular, Inc., St. Paul, MN) [5], and the OPTIMIZER™ III (Impulse Dynamics USA, Inc., Orangeburg, NY) [6, 7•, 8•].

Biventricular pacing, or resynchronization therapy, has been shown to improve LV systolic function and quality of life in patients with HF [4,9]. The degree of improvement in LV function based on EF is approximately 4% and appears within 6 months of therapy initiation [10]. Although electrocardiogram QRS duration is used to predict which patients have LV mechanical dyssynchrony it has been reported as being less than perfect [11,12]. Some studies suggest that restoration of synchronization may not be the only mechanism leading to clinical improvement [13]. QRS duration remains important in the selection of patients for CRT. It is estimated that only a quarter of patients with HF have a prolonged QRS duration and may be eligible for this form of therapy [14,15]. Therefore, a device-based therapy needs to be developed that can safely improve LV contractile function in patients who have a normal activation sequence but advanced HF despite optimal medical therapy. One such device is the Impulse Dynamics cardiac contractility modulation (CCM) system. This review examines some novel thinking as to the mechanism of action of this investigational form of therapy. It addresses the effects of this form of therapy in preclinical studies in animals with experimentally-induced HF as well as early clinical findings in patients with advanced HF.

Table 1. mRNA expression of SERCA2a, NCX, and GATA4 and expression of phosphorylated phospholamban in LV myocardium of normal dogs, dogs with untreated HF, and dogs with HF treated short-term with CCM electrical signals

	Normal	Untreated HF	HF + CCM
Phosphorylated phospholamban, *du*	2.83 ± 0.20	1.97 ± 0.10*	4.19 ± 0.45†
mRNA expression of SERCA2a, *du*	920 ± 28	110 ± 4*	617 ± 11†
mRNA expression of NCX, *du*	30 ± 2	98 ± 14*	48 ± 4†
mRNA expression of GATA4, *du*	103 ± 31	204 ± 19*	160 ± 26†

CCM—cardiac contractility modulation; du—densitometric units; HF—heart failure; LV—left ventricular; NCX—sodium-calcium exchanger; SERCA2a—sarcoplasmic reticulum ATPase-dependent calcium pump.
*$P < 0.05$ vs normal.
†$P < 0.05$ vs untreated HF.

Mechanism of Action of CCM Therapy

CCM therapy is based on the delivery of electrical signals to the LV myocardium during the absolute refractory period. These so-called CCM signals contain approximately 150 times the amount of energy delivered during a standard pacemaker impulse. The CCM signals do not initiate contraction, they do not recruit additional contractile elements, and there is no additional action potential as would be observed with paired pacing or post-extrasystolic potentiation. Therefore, CCM signals are referred to as "nonexcitatory." Initial studies performed in isolated superfused normal papillary muscles and isolated normal ferret hearts suggested that CCM signals influence calcium entry into the cardiomyocyte and, in doing so, influence contractility [16,17]. Subsequent studies, however, performed in dogs with experimentally induced chronic HF indicated that the improvement in LV function may be related to alterations in sarcoplasmic reticulum (SR) calcium cycling mediated by the delivery of CCM signals [18,19]. HF is associated with abnormalities in the expression of genes encoding SR calcium handling proteins and post-translational modification of their associated proteins. Some commonly identified key abnormalities include downregulation of genes encoding for the SR ATPase-dependent calcium pump (SERCA2a) [20–24], changes in expression and phosphorylation of phospholamban [23–27], and altered regulation of the sodium-calcium exchanger (NCX) [20,27,28]. Therefore, treatments aimed at improving gene and protein expression of SR calcium cycling proteins in HF would be considered therapeutic.

Results of recent studies conducted in normal dogs, dogs with untreated coronary microembolization–induced HF, and dogs with HF treated for 4 hours with CCM signals delivered to the LV anterior wall support the concept that CCM therapy normalizes SR calcium cycling proteins. For example, LV anterior wall tissue obtained from normal dogs compared with LV anterior wall tissue of dogs with untreated HF showed a significant reduction in phosphorylated phospholamban. In contrast, dogs that were treated for 4 hours of continuous therapy with CCM signals in the LV anterior wall had normalization of phosphorylated phospholamban (Table 1) [18,20]. This improvement in phospholamban phosphorylation was associated with increased expression of SERCA2a (Table 1) [20]. In addition to the improvements in SR function, CCM therapy also normalized mRNA expression of the NCX, its phosphorylation, and its transcription factor GATA4 (Table 1) [29,30]. These short-term findings, when coupled with identical long-term observations of LV tissue obtained from dogs treated for 3 months with CCM signals (unpublished observations), support the belief that normalization of SR calcium cycling and possibly of the NCX are key mechanisms that underlie the improvement in LV contractile function observed with short and long-term CCM therapy.

Effects of CCM Therapy in Dogs with HF

Dogs with microembolization-induced HF treated for 6 hours with continuous CCM electrical signals, through leads implanted on the epicardial surface of the LV during the absolute refractory period, had a significant improvement in LV ejection fraction (LVEF). In this short-term study, LVEF increased from 31 ± 1% at baseline to 44 ± 2% 6 hours after initiation of therapy ($P < 0.001$) [7•]. The improvement in LVEF was associated with a significant increase in stroke volume and a significant decrease in LV end-diastolic pressure [7•]. In this study, continuous delivery of CCM signals had no effect on QTc interval and was not associated with any chronotropic and/or proarrhythmic effects.

In a second study conducted in six dogs with intracoronary microembolization-induced HF, CCM electrical signals were delivered using a lead implanted in the distal anterior coronary vein. The CCM lead was advanced into the vein via the coronary sinus in a manner similar to that used with CRT [8•]. In this study, CCM signals were delivered continuously for 6 hours daily for a duration of 3 months (a daily duty cycle of 6 hours on and 18 hours off.) The results were compared with those of six HF control dogs in which no therapy was implemented for the same follow-up duration period of 3 months. In control dogs, LVEF decreased from 28 ± 1% to 23 ± 1% ($P < 0.001$). In contrast, in dogs treated with CCM, LVEF increased from 31 ± 1% to 34 ± 2% $P < 0.04$). The improvement in EF in CCM-treated dogs was associated with a significant decrease in LV

end-diastolic pressure and a significant increase in stroke volume. As with the short-term study, CCM therapy had no effects on QTc duration and was not associated with any chronotropic effects or proarrhythmic effects [8•].

In a third series of experiments conducted in dogs with intracoronary microembolization-induced HF, the effects of short-term CCM therapy on myocardial oxygen consumption (MVO_2) was examined. In this series of experiments hemodynamic parameters and myocardial oxygen consumption were measured in an open chest, anesthetized state, with epicardial electrodes used to administer CCM signals continuously for 2 hours [31]. Heart rate and peak LV pressure did not change significantly with CCM therapy. Two hours of CCM therapy significantly decreased LV end-diastolic pressure and significantly increased LVEF from 34 ± 1% to 42 ± 2% ($P < 0.001$) [31]. A particularly important observation in this study was the improvement in LV systolic function accompanied by unchanged total LV coronary blood flow and unchanged MVO_2. In a recently completed study in dogs with HF, long-term (3 months) therapy with CCM electrical signals was delivered from leads positioned on the right interventricular septum with an implantable signal generator (Impulse Dynamics OPTIMIZER II™), a device similar to a pacemaker-internal cardiac defibrillator. In this study, CCM signal delivery resulted in a significant improvement in LVEF, a significant increase in stroke volume, a decrease in MVO_2, and an increase in LV mechanical efficiency [32].

Effects of CCM Therapy in Patients with HF

In safety and feasibility studies conducted in patients, CCM signals are delivered to the myocardium by an implanted device that looks like a pacemaker and connects to the heart via standard commercially available pacing leads. The device, called the OPTIMIZER™ System [33•], does not have pacing or antitachycardia therapy capabilities but is designed to work in concert with pacemakers and internal defibrillators. The originally investigated systems had a fixed battery which, because of the high energy delivered with each CCM pulse, had longevity of 6 to 8 months. Recently, a system with a rechargeable battery has been introduced (OPTIMIZER-III). With this new system, a patient recharges the battery at home once a week via a transcutaneous energy transfer charging unit.

The first safety and efficacy results with chronic CCM signal applications were obtained in patients with NYHA Class III symptoms and QRS duration ≤ 120 ms [34•]. The study was an unblinded, uncontrolled, treatment only feasibility study designed mainly to test the functionality of the OPTIMIZER™ System. In this study, the OPTIMIZER™ System was implanted in 23 patients who were predominantly male (92%) with an average age of 62 ± 9 years and were split between idiopathic and ischemic cardiomyopathy (41% and 59%, respectively). Baseline EF was 22 ± 7% and the average Minnesota Living with Heart Failure Questionnaire score averaged 43 ± 22%. Patients were well medicated with diuretics (88%), β-blockers (88%), and angiotensin-converting enzyme inhibitors (100%.) The study showed operation of the device as intended. There was no change in intrinsic ambient ectopy observed between baseline and 8 weeks of treatment and no overt safety concerns. Improvements were reported in patient symptoms (assessed by NYHA class), quality of life (assessed by Minnesota Living with Heart Failure Questionnaire), and LVEF [34•].

Two multicenter, randomized controlled studies of CCM are currently underway. One study is in Europe and the other is in the United States, with the latter being performed under an investigational device exemption from the US Food and Drug Administration to definitively test the safety and efficacy of CCM as a treatment for HF. The safety evaluations include examination of mortality, hospitalizations, proarrhythmic effects, signs of progressive HF, and overall incidence and severity of adverse events.

Conclusions

Preclinical studies conducted to date in dogs with experimentally induced HF indicate that CCM therapy, whether short term or long term, is associated with improved SR calcium cycling and improved LV contractile function. The improvement in LV function occurs in the absence of an increase in MVO_2 a desirable feature for any therapy aimed at improving cardiac contractility in the setting of HF. The absence of an increase in MVO_2 in the face of an increase in cardiac contraction strongly argues in favor of a mechanism of action of CCM therapy that is independent of calcium entry into the cell. Preliminary studies in patients with HF are encouraging. Evidence available at this time suggests that CCM therapy appears to be safe and devoid of chronotropic and proarrhythmic effects. The efficacy trends favor improvement in LV function as well as in quality of life. The overall safety and efficacy of this form of treatment are being tested in randomized controlled clinical trials. If these studies show CCM treatment in HF patients to be safe and effective, a new, easily deployable treatment will be made available to patients with otherwise untreatable HF symptoms.

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