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Electrical Modulation of Cardiac Contractility: Clinical Aspects in Congestive Heart Failure

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Abstract. **Heart failure is a highly prevalent disease in western society. Drug therapies aimed at increasing myocardial contractility have been associated with decreased survival. Several short and mid term clinical studies have suggested adjuvant or alternative therapies to congestive heart failure using modified pacing techniques that were aimed to increase contractility (e.g. Paired pacing) or restore synchrony of contraction (biventricular pacing). While delivery of paired pacing was abandoned during the early 70's, biventricular pacing has recently emerged as an adjuvant treatment to limited group of congestive heart failure patients with aberrant left ventricular conduction. In this brief review, we describe our initial safety and efficacy experience in patients with heart failure using a novel non-stimulatory electrical approach to the delivery of positive inotropic therapy to the failing myocardium. The study suggests that unlike modified pacing techniques, delivery of the signal to the left ventricle during the refractory period resulted in a rapid increase in myocardial contractility and improved hemodynamic performance. The near instantaneous contractility improvement achieved by this type of stimulus was shown to be safe and effective independently of the primary cause of heart failure or the function of the conduction system. Unlike pharmacologic treatments, which have a relatively constant effect, use of electrical stimuli may prove useful as a new therapeutic modality in the treatment of heart failure with which contractility can be improved when and as needed.**

Key Words. **heart failure, electric signals, hemodynamic effect**

Introduction

Chronic heart failure has reached epidemic proportions in the United States. The syndrome affects over 5 million people with over 450,000 new cases diagnosed each year and over 250,000 deaths [1,2]. The prognosis of heart failure is poor; nearly 50% of all patients die within five years of diagnosis despite optimal conventional treatment [3,4,5]. Left ventricular dysfunction once established as a result of a primary insult such as myocardial infarction, can ultimately lead to chronic heart failure. Activation of intrinsic compensatory mechanisms initially enable the left ventricle to improve cardiac output and perfusion pressure in the face of reduced myocardial contractility. Compensatory mechanisms that include sustained neurohumoral activation can lead to progressive deterioration of residual functional cardiac units which places additional burden on overall cardiac performance. The management of heart failure has evolved considerably over the past two decades. Many pharmacological agents which have been developed to increase the contractility in the failing heart, produced impressive hemodynamic effects, but

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long term therapy has failed to produce clinical benefits and has increased mortality in treated patients [6,7]. This experience has led many physicians to suggest that positive inotropic therapy be abandoned as a therapeutic approach for heart failure [8]. Heart failure is nowadays considered to be governed and impelled by neurohumoral imbalances and by intracardiac paracrine processes [9]. Experimental evidence suggests that excessive adrenergic stimulation of the heart may actually contribute to the untoward natural history of congestive heart failure via basic mechanisms of catecholamine-mediated cardiac toxicity [10]. Thus prolonged activation of the sympathetic nervous system in patients with impaired ventricular function exerts adverse effects on the heart and circulation by a variety of mechanisms [9,10,11].

Therefore, the capability of electrically modulating myocardial contractility on a beat-by-beat basis fulfils a clinical need in the treatment of heart failure patients, since it also has the potential for diminishing the elevated sympathetic tone, alleviating adrenergic adverse effects (i.e. precipitating cardiac arrhythmias, elevating systemic vascular resistance and elevating afterload) as well as the induction of phenotypic changes in the myocardial and in the vascular smooth muscle.

Paired pacing

In 1898, Langendorf described the Post Extra Systolic Potentiation phenomenon (PESP), i.e. contraction augmentation of the beat succeeding extrasystole [12]. Following the discovery that PESP increases myocardial contractility even in the failing ventricle, paired pacing was applied, producing an extrasystole every other beat, effecting continuous contractility augmentation.

Although numerous studies have reported increased inotropy in the failing ventricle, investigative enthusiasm declined by the end of the 1960's as adverse effects were discovered. Adverse effects included increased risk for ventricular arrhythmia, and risk of increased ventricular failure [13,14,15].

Bi-ventricular pacing

Recent short and mid-term clinical trials using pacing have shown improved hemodynamics in patients with heart failure, and are being explored as adjuncts to traditional pharmacologic therapies [16,17,19,20,21]. Optimization of AV delay while pacing the right ventricle showed some improvement in cardiac performance. Hemodynamic and symptomatic improvement resulted also from reduced mitral regurgitation and longer ventricular filling time [18,19,22]. However, ventricles with normal intraventricular conduction respond to right ventricular pacing with lengthened and aberrant propagating wavefronts. Moreover, there is some concern regarding the lack of coordination between the septum and other contracting walls [23,24,25,26]. When only the right ventricular apex is paced, the septum and segments of the left ventricular anterior wall may become dyskinetic. Accordingly, as mechanical contractions become deficient, a hemodynamic deterioration ensues. Thus, placement of the left ventricular free wall electrodes, as is the case with biventricular pacing, allows a parallel activation with the septum, and restores cardiac output. The application, however, is limited to a fraction of patients with heart failure that manifest long QRS complex.

In the present review, we will discuss initial safety and efficacy results of a novel approach for increasing contractility of the failing left ventricle by the delivery of non excitatory electric signals.

These cardiac contractility modulating (CCM) signals applied during the refractory period of each heartbeat neither initiate a new heart beat nor modify the activation sequence within the ventricles. CCM signals have shown positive inotropic effects in rabbit papillary muscles and isolated hearts, and in experimental models of chronic heart failure in dogs [27,28]. The contractility enhancement achieved by this modality allows titration to the momentary needs of the patient by varying the characteristics of the electrical signal and could serve as the basis for a new approach for treating patients with low cardiac contractility

Patient population and study design

The data presented here originated from a prospective, acute study designed to assess cardiac hemodynamics of patients with heart failure in response to CCM signal delivery. Heart failure patients with ejection fraction (EF) below 35% having either ischmic or idiopathic dileted cardiomyopathy and were candidates for an EP study were included in the protocol. All patients provided written informed consent prior to the study. Exclusion criteria were: patients with implanted pacemaker or defibrillator, patients with advanced NYHA class IV on intravenous inotropic support, patients with unstable angina, and patients actively treated with Class I or Class II anti-arrhythmic agents.

The clinical characteristics of the patients are shown in Table 1. Fifteen patients (12 males and 3 females, mean age 62 ± 8 years, NYHA class 2.1 ± 1, and left ventricular ejection fraction $28 \pm 5\%$) were studied. Ischemic or dilated cardio-

Table 1. *Demographic characteristics of patient study group. C/A = cathode to anode distance on multipolar lead measured in centimeters; ICM = ischemic cardiomyopathy; IDC = idiopathic dilated cardiomyopathy; Class = New York Heart Association classification; EF = left ventricular ejection fraction at entry into the study.*

Subject #	Lead Position	C/A (cm)	Type	Class	Age	Gender	EF
1	Anterior	1	ICM	II	63	M	35
2	Lateral	1	ICM	II	63	M	34
3	Anterior	0.5 1	DCM	II	64	M	30
4	Anterior	0.5 1	DCM	II	51	M	25
5	Lateral	1	ICM	III	54	F	25
6	Posterior	0.5 1	DCM	I	68	M	30
7	Anterior	0.5 1.5	DCM	I	66	F	30
8	Posterior	0.5 1.2 2.2	DCM	II	48	M	20
9	Lateral	1.2	DCM	II	57	M	25
10	Anterior	1	ICM	II	68	M	35
11	Lateral	1.2 3	ICM	II	71	M	30
12	Anterior	1.2 1.7 3.2	ICM	II	71	M	35
13	Anterior	1.7 2.8	ICM	III	55	M	20
14	Post-latl	2.4	DCM	III	71	F	25
15	Anterior	1.7	DCM	III	64	M	22

myopathy were present in similar proportions. Among the 15 patients, 4 had a previous diagnosis of ventricular tachycardia and/or atrial fibrillation. Seven of the patients had functional mitral regurgitation. All patients underwent a transthoracic echocardiographic study prior to formal entry into the study to determine left ventricular ejection fraction. In addition to establishing the extent of regional left ventricular wall motion abnormalities, the echocardiogram was also used to select the target vein for placement of the transvenous multipolar electrode.

On the day of the study, two myocardial pacemaker leads (model TPW42, 2-0 braided steel, Ethicon, Somerville, NJ, USA) were inserted into the right atrium and right ventricle via the femoral or subclavian route. The left ventricle was accessed retrograde via the coronary sinus with an octopolar (spanning 3.8 cm) Revelation 3.3 F catheter (Cardima, Freemont, CA). The catheter was advanced into the distal anterior-interventricular (n = 8), lateral (n = 4), or posterior (n = 3) epicardial vein. Flouroscopic examination and intracardiac electrocardiograms were performed to confirm positioning of the electrode. All studies were performed during concomitant DDD pacing during both baseline and CCM signal delivery.

Of the eight existing rings located on the multipolar lead, two were selected for sensing local electrical activity (10.3 mm^2, 2 mm apart) and another two for delivering of the CCM signal.

Aortic and left ventricular pressures were measured with 5 F catheter-tip dual sensor (12 cm apart) micro manometer placed in the left ventricle and aorta, (Millar Instruments, Houston, TX). Peak left ventricular rate of change of pressure during isovolumic contraction, peak + dP/dt, was derived from the left ventricular phasic waveform using digital differentiation. The following physiologic parameters were calculated: left ventricular peak systolic pressure, aortic pulse pressure, peak left ventricular + dP/dt

The CCM signal generator

The CCM signal generator used in this initial clinical study called the 'SCEPTER' was designed to deliver CCM signals with or without pacemaker support. The system can be programmed to sense the activity in the muscle tissue in the area adjacent to the electrodes, process it and generate CCM signals with predefined electrical waveforms in voltage or current form [22]. Built-in safety-designed algorithms inhibit the generation of the CCM signal when irregular electrical activity is detected, as in the case of premature atrial or ventricular complexes.

Hemodynamic and echocardiographic findings with application of the CCM signal

Fig. 1 illustrates typical waveforms of left ventricular pressure and rate of change of pressure (dP/dt) in a patient with heart failure before and during application of the CCM signal. The average hemodynamic changes of all 15 patients are depicted in Fig 2. On average, CCM signal application significantly improved left ventricular systolic pressure, aortic pulse pressure and peak + dP/dt. In all cases, the global positive inotropic effects developed early and reached a steady state within a few minutes. No significant difference in the effect of CCM signal could be observed between patients having ischemic or idiopathic cardiomyopathy.

Echocardiograms were obtained at baseline (control) and during CCM signal application in 10 of 15 patients. At a regional level, the anterior wall and septum showed visible improvements in systolic thickening in patients with leads placed in the anterior inter-ventricular vein suggesting a localized effect of the CCM signal. Fig. 3 illustrates the beat-to-beat improvement in septal wall motion velocity in a patient before and

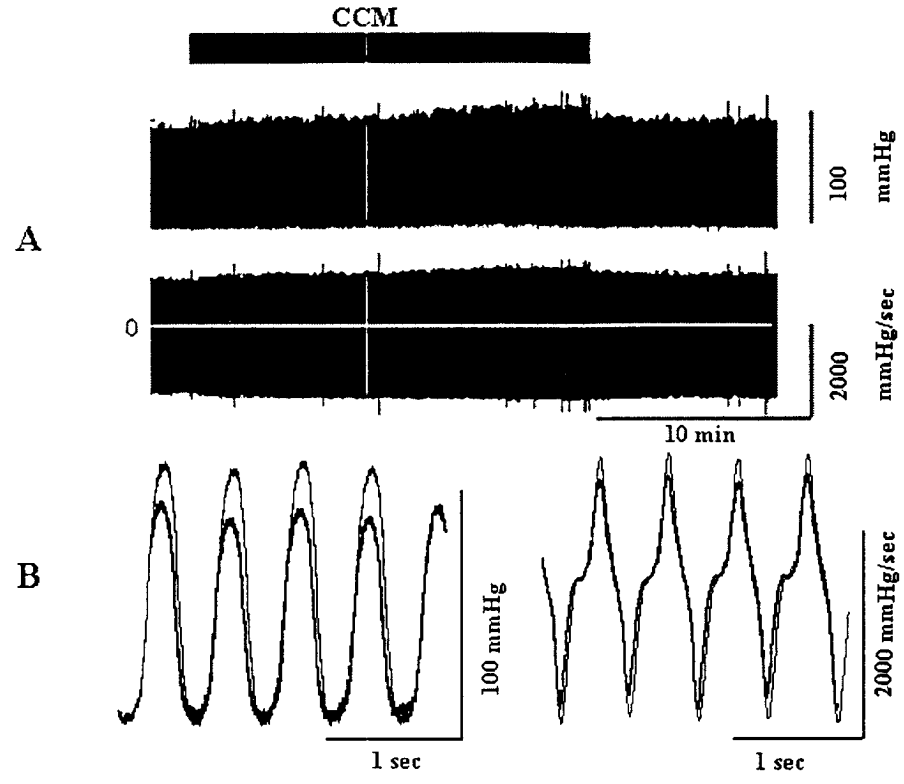

Fig. 1. *Increase in left ventricular pressures during CCM application: A. Left ventricular waveforms (upper panel) and derivative of left ventricular pressure + dp/dt (lower panel). The signal is delivered to a female patient with idiophatic cardiomyopathy having an ejection fraction of 25%. Upon the turn on of the CCM signal a gradual increase in left ventricular pressure with an average of 13.3% can be observed. Pressure derivative (dp/dt) also increased by 15.6%. When the signal is turned off both waveforms return to baseline. B Left ventricle pressure waveform (left panel) together with its derivative (right panel) in an enlarged scale. The baseline waveforms (Thick lines) are superimposed on waveforms during CCM delivery. The changes in both LVP and dp/dt are clearly demonstrated.*

during application of the CCM signal. Five of 15 patients in whom echocardiogram quality allowed accurate evaluation of left ventricular ejection fraction before and during CCM application showed an average increase of ejection fraction of 16 % during CCM application compared to baseline control.

Electrocardiographic effects of DDD pacing and CCM signal application

The P-R interval duration and intrinsic conduction patterns were not significantly altered by delivery of the CCM signal. DDD pacing alone altered ventricular depolarization with clear changes in QRS duration ($102 + 29$ ms to 186 ± 38 ms) CCM signal delivery did not alter QRS duration, a feature that denotes the non-excitatory nature of the signal. There was no relationship between percent improvement in left ventricular contractility enhancement, measured by dp/dt, during the application of the CCM signal and the A-V delay (Fig. 4), indicating that the derived benefit from CCM signal application was independent of A-V delay. Application of CCM signal did not increase arrhythmias rate (Fig. 5). Further, there is a tendency to decrease arrhythmias rate during the period of CCM signal delivery.

Conclusions

These results of acute CCM signal delivery in patients with heart failure suggest that this novel form of therapy can elicit improvements in the global contractile state of the failing left ventricle. Based on these results one can speculate that the incorporation of this technology into implantable pacemakers and/or defibrillators will enhance the therapeutic usefulness of these systems for the treatment of heart failure. The ability of CCM signal delivery to provide positive inotropic support to the failing heart 'on demand', provides a new approach that, when coupled to optimal medical therapy, may result in improvement of quality of life of this ever increasing

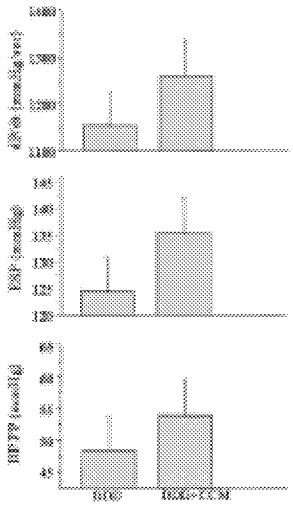

Fig. 2. *Average effect of CCM signal: Bar graphs showing the average change (±SE) in peak left ventricular systolic pressure (top), peak left ventricular + dP/dt (second panel) and aortic pulse pressure (bottom panel) during DDD pacing alone and during DDD pacing combined with CCM signal. Left ventricular dp/dt increased from 1158±68.9 mmHg/sec to 1261±76.1 mmHg/sec. LV systolic pressure increased from 124.5±6.2 mmHg to 135.5±6.3 mmHg and pulse pressure increased from 48.5±5.3 mmHg to 54.1±5.4 mmHg. All changes were significant ($p < 0.05$).*

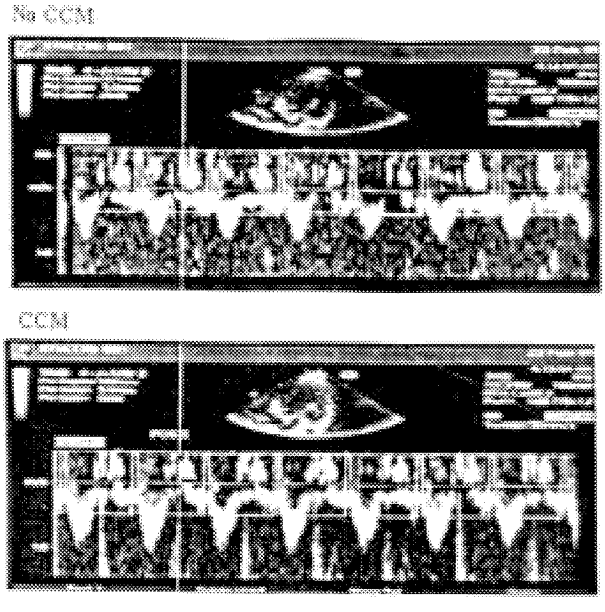

Fig. 3. *Echocardiograpic traces of septal wall motion. Septal wall motion velocity in a patient with idiophatic cardiomyopathy (EF 20%) was measured using echo doppler. CCM signal was delivered to the Anterior interventricular vein (GCV). Motion before delivering the CCM signal (upper trace) was compared to motion when CCM signal was applied (lower trace). A visible improvement of septal movement is demonstrated during CCM delivery.*

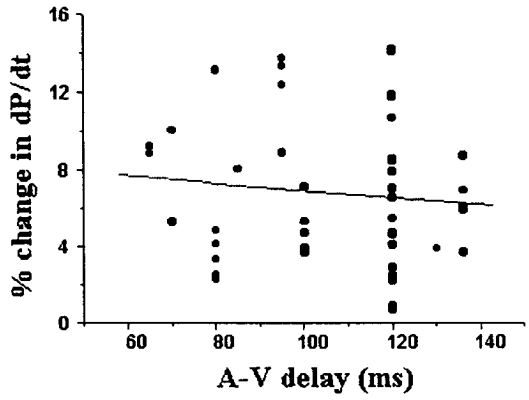

Fig. 4. *Relationship between atrio-ventricular (AV) pacing delay and the increase in left ventricular peak dp/dt during CCM application. There is no apparent relation between AV delay and increase in contractility ($P = 0.483$ NS).*

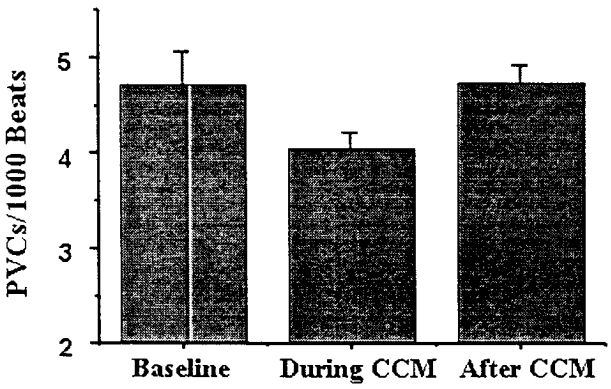

Fig. 5. *Change in the rate of arrhythmias during CCM delivery: Rate of arrhythmias was assessed at baseline, during, and after the delivery of CCM signal. Rate of arrhythmias significantly decreased ($P < 0.05$) during the delivery of CCM and returned to approximately baseline level after the signal was turned off. Arrhythmia rate was calculated as the number of ectopic beats per 1000 heart beats.*

patient population. Additional studies are needed to further evaluate the efficacy and safety of this form of therapy in patients with heart failure.

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