Heart Resynchronization in CHF Patients with Dilated Cardiomyopathy Using a Rate-Responsive Pacemaker Controlled by the Autonomic Nervous System

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Summary

In this study, four patients with congestive heart failure (CHF) due to dilated cardiomyopathy were treated with a heart resynchronization therapy in combination with the Closed Loop Stimulation (CLS) rate-adaptive pacing. Before the implantation, the patients had a prolonged PR-interval and the left bundle branch block. The heart resynchronization has been achieved by a dual-chamber CLS pacemaker. A unipolar Y-adapter was plugged in the ventricular port of the pacemaker. The right ventricular lead was connected to the negative pole (cathode) and the left ventricular lead to the positive pole (anode) of the Y-adapter, while the atrial lead was connected to the atrial port. The patients were evaluated before pacemaker implantation, after the first 15 days and 30 days after pacemaker implantation, and every 3 months thereafter. All patients exhibited a clear improvement in the ejection fraction and cardiac output, a greater exercise capacity, and a decrease in the diastolic diameter of the left ventricle after pacemaker implantation. In all but one patient, the duration of the QRS-complex was reduced.

Key Words

Congestive heart failure (CHF), heart resynchronization, Closed Loop Stimulation (CLS)

Introduction

Congestive heart failure (CHF) is the leading cause of death in the Western world and has reached epidemic proportions. In the USA alone, from 1970 to 1990, the incidence of this condition has increased from 250,000 to 400,000 new cases each year. It is assumed that about five million Americans have this disease [1]. There is a relationship between the severity of the disease and the death rate at the end of one year. Patients in NYHA-functional class II present a death rate between 5 and 15 %, with 50 to 80 % of these casualties being unexpected. Patients in functional class IV present an annual death rate of 30 – 70 %, from which 5 to 30 % are unexpected [2, 3]. The cost of this disease in the USA is estimated to be around $38 billion. The major physiological changes that lead to CHF are mechanical dysfunction and disturbances in the conducting system and neurohumoral activation. The heart stimulation therapy initially described by Hochleitner in 1990 [4] has evolved into right ventricular bifocal stimulation [5] and biventricular multisite stimulation [6]. The effects of biventricular multisite stimulation, which is called Heart Resynchronization Therapy, have shown a better quality of life and an improved exercise capacity [7,8]. Recent studies have demonstrated that, under this therapy, the death rate has declined significantly [9,10].
This article presents follow-up results for four patients who received a pacemaker combining atrial synchronous biventricular pacing with the Closed Loop Stimulation (CLS) rate-adaptive principle.

Materials and Methods

Between July and October, 2000, the Inos^{2+} CLS pacemaker (Biotronik, Germany) was implanted in four patients suffering from CHF caused by dilated cardiomyopathy of idiopathic etiology. The patients had been treated with a complete drug regimen and hospitalized more than three times over the 6 months preceding the implantation. The patient age ranged from 48 to 75 (mean 59.5 years) and two were males. All

			Before implantation					After implantation				
Patient	**Age**	**Gender**	**EF (%)**	**FS (%)**	**LVDD (cm)**	**CO (l/min)**	**NYHA class**	**EF (%)**	**FS (%)**	**LVDD (cm)**	**CO (l/min)**	**NYHA class**
1	48	m	37	14	7.1	4.4	IV	44	17	6.9	2.4	I
2	59	m	35	12	7.2	1.8	IV	48	19	6.7	4.2	II
3	75	f	26	9	6.2	3.6	IV	59	25	6.3	6.5	I
4	56	f	36	13	6.5	3,8	III	48	24	5.9	5.2	II
Mean	59.5		33	8.75	6.75	3.4	3.75	50	21.3	6.45	4.6	1.5

Table 1. Clinical characteristics of the studied patients and echocardiographic values before and after implantation of a biventricular pacemaker system. EF = ejection fraction; FS = fractional shortening; LVDD = left ventricular diastolic diameter; CO = cardiac output.

patients had a prolonged PR-interval and the left bundle branch block, with the QRS-complex varying between 170 and 200 ms (mean 185 ms). According to Doppler-echocardiographic evaluation, the end-diastolic diameter of the left ventricle ranged from 6.2 to 7.2 cm (average 6.75 cm) in different patients, and the ejection fraction varied between 26 and 37 % (average 33 %). The cardiac output was 1.8 – 4.4 l/min (mean 3.4 l/min) (Table 1).

The covered distance during the 6-minute walk test varied between 180 and 480 m (mean 300 m). An initial heart rate during the test was 88 – 100 beats/min and a final heart rate 104 – 130 beats/min. In the ergometry evaluation, the distance covered varied between 357 and 426 m (average 400 m), and the duration of the test between 8'14'' and 9'23''. The maximum achieved heart rate varied from 94 to 163 beats/min (average 125 beats/min). At the time of pacemaker implantation, three patients were in NYHA-functional class IV, and one in III.

Heart resynchronization therapy was begun to treat heart failure without any indication of being due to a disturbance in the conducting system. First, a passive fixation endocardial lead (Polyrox 60 BP, Biotronik) was implanted in the right ventricle. Thereafter, an active fixation endocardial lead (YP 60 BP, Biotronik) was inserted into the right atrium. R- and P-wave amplitudes, ventricular and atrial pacing thresholds, and lead impedance were measured. Finally, a third lead was introduced in the coronary sinus through the same puncture (Corox LV 75-UP, Biotronik) and advanced into the left-side vein (three patients) or the posterior vein (one patient).

All four patients received the Inos^{2+} CLS pacemaker that integrates the CLS rate regulation into the autonomic nervous system control. The pacemaker measures the impedance variation caused by differing degrees of myocardial contractility in the right ventricle. A unipolar Y-adapter was plugged into the ventricular port of the implanted pacemakers. The right

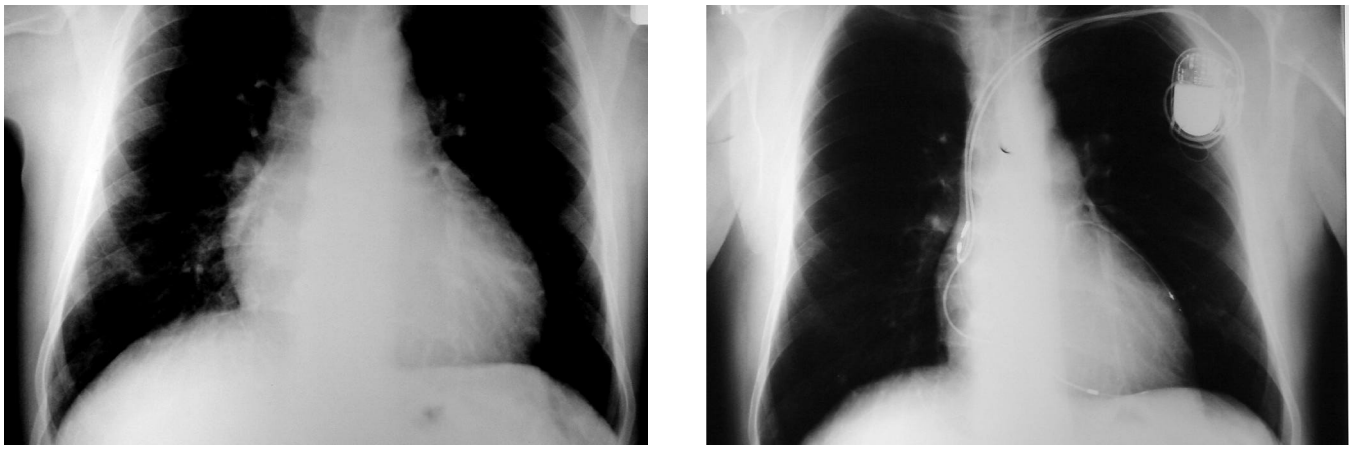


Figure 1. X-ray pre- (panel a) and post-implantation (panel b) of a biventricular pacemaker system (male patient, aged 48).

ventricular electrode was then connected to the negative pole (cathode) and the left ventricular electrode to the positive pole (anode) of the Y-adapter (i.e., of the ventricular channel). This configuration allows the pacemaker to measure the right ventricular intracardiac impedance in the usual way – between the cathodal connector of the ventricular channel and the pacemaker housing. The right atrial lead was connected to the atrial channel of the pacemaker. The total time of surgery varied between 42 and 252 min.

An X-ray of the implanted biventricular device can be seen in Figure 1. The arch of the radioscopic equipment is placed in such a way that the visualization position remains front-left oblique, so that the coronary sinus location reference can be the upper third of the curve of the lead positioned in the right ventricle, with the electrode tip in the opposite direction to the one inserted in the ostium.

Following pacemaker implantation, the pacing mode was programmed to DDD-CLS (i.e., DDDR mode according to the CLS principle). The basic rate was programmed to 60 beats/min, the maximum CLS rate to 150 beats/min, and a dynamic adaptation of the atrioventricular interval was enabled. The bipolar configuration was used for pacing and sensing.

Results

The patients were evaluated within the first 15 days and at one month after pacemaker implantation, and every 3 months thereafter. In three patients, there was a decrease of the QRS-complex duration to 100 – 120 ms (mean 110 ms). The ejection fraction measured between 9 and 12 months after implantation varied between 44 and 59 % (mean 49 %). The end-diastolic diameter of the left ventricle varied between 5.9 and 6.9 cm (mean 6.4 cm) and the cardiac output between 4.2 and 6.5 l/min (mean 5.1 l/min). The data from the 6-minute walk test is shown in Table 2. The distance covered ranged between 300 and 712 m (mean 406 m), which represented 43 % improvement, on average, compared to the period before pacemaker implantation. In the ergometry evaluation, the covered distance varied from 300 to 712 m (average 431 m), the test duration from 10'28" to 14'12", and the maximum achieved rate ranged from 133 to 173 beats/min (mean 143 beats/min) (Table 3).

Already at 1 month after pacemaker implantation, two patients were in NYHA-functional class I and two in class II (Figure 2). Although there was a clinical improvement in the single patient who exhibited no decrease in the QRS-complex duration at 15 days after implantation, we attempted to relocate the lead from the front vein to the side left vein. However, a stable position could not be found. The patient was thereafter subjected to a mini-thoracotomy, to implant an epimyocardial lead on the side surface of the left ventricle. This resulted in a QRS-complex decrease to 100 ms (Figure 3). This patient was thereafter followed in the same manner as other three patients.

Discussion

Biventricular pacing has shown positive results in terms of improving a patient's functional class and increasing his or her capacity for physical exertion. The influence of this pacing mode, which effects heart resynchronization, may be a factor in improving mechanical dysfunction and in partially correcting conduction disturbances that affect neurohumoral activation. Two recent studies have clearly demonstrated that this therapy also influences the rate of patient survival [9,10].

On the other hand, drug treatment has two different objectives: first to relieve symptoms (diuretics, digox-

	Before implantation			After implantation		
Patient	Distance (m)	Min heart rate (beats/min)	Max heart rate (beats/min)	Distance (m)	Min heart rate (beats/min)	Max heart rate (beats/min)
1	480	100	130	712	80	120
2	250	96	108	364	70	96
3	180	92	104	300	60	96
4	292	88	124	350	80	122
Mean	300.5	94.0	116.4	431.5	72.5	108.5

Table 2. Distance covered during a 6-minute walk performed before and after implantation of a biventricular pacemaker system.

	Distance (m)		Duration		Max heart rate (beats/min)		BP (mmHg) Baseline		Exercise		Recovery	
Patient	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
1	426	852	8'14"	14'12"	163	173	120 80	140 80	153 82	198 86	125 80	132 76
2	413	652	9'23"	13'41"	94	113	80 60	120 80	100 60	110 60	100 60	110 60
3	403	698	8'41"	12'36"	134	148	100 70	130 80	125 75	160 80	120 75	140 70
4	357	586	8'34"	10'28"	112	140	105 75	125 75	130 60	170 85	90 60	135 80
Mean	400	697	8'31"	12'29"	126	143	101 71	129 79	127 69	159 78	109 69	129 71

Table 3. Results of a treadmill exercise before (pre) and after implantation of a biventricular pacemaker system (post). Systolic and diastolic blood pressure (BP) values are shown for each setting.

in and vasodilating agents), and second to decrease the progression of remodeling of the left ventricle (ACE inhibitors, hydralazine, isosorbide dinitrate, and beta-blockers). The latter medications act fundamentally on the neurohumoral activation and have changed the history of the treatment [11]. These drugs also aim at maintaining the average arterial pressure by involving the sympathetic nervous system, the renin-angiotensin system, and increased antidiuretic hormone production in response to cardiac output decrease, as compensatory mechanisms for maintaining the average arterial pressure [12].

Conduction disturbances secondary to a heart failure prolong interatrial conduction [13], PR-intervals [14], and interventricular conduction [15]. Wilensky et al. reported that 82 % of patients exhibited significant disturbances in the interventricular conduction within 60 days before their death, as compared with 68 % conduction disturbance rate found at earlier ECG evaluations. During an evaluation period of > 2 years, the duration of the QRS-complex increased to 100 ± 20 ms in the first phases and to 130 ± 30 in the last phases of the follow-up. Complete heart block was identified in 38 % of the patients, with a high prevalence of the complete left-branch block [15]. The hemodynamic consequences of the electrical disturbances are augmented mitral and tricuspid regurgitation and a reduced filling time in the left ventricle, which in turn jeopardizes the compensatory Frank-Starling mechanism. Moreover, impairment of the mechanical function secondary to the systolic and/or diastolic heart dysfunction gives rise to a decrease in cardiac output and in average arterial pressure if the neurohumoral system unchain compensatory mechanisms [16]. In a recent study, Martino et al. correlated the neurohumoral behavior in patients implanted with a cardiac pacemaker with a closed-loop sensor controlled by the autonomic nervous system. They demonstrated the physiological behavior of heart-rate restoration as a response to a decrease in vascular systemic resistance in patients with chronotropic failure and dual-chamber pacemakers, as well as the normalization of the response and the neurohumoral function of the patients with a normal sinus function even during ventricular pacing [17].

Due to the relationship between the $Inos^{2+}$ CLS pacemaker sensor and neurohumoral activation, this system was chosen in order to delay left-ventricular remodeling in patients with CHF caused by dilated cardiomyopathy.

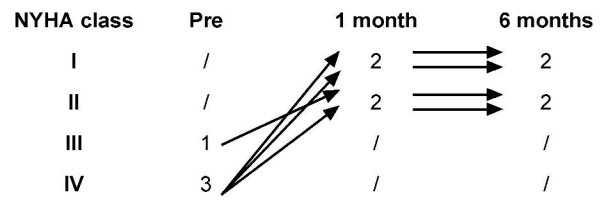
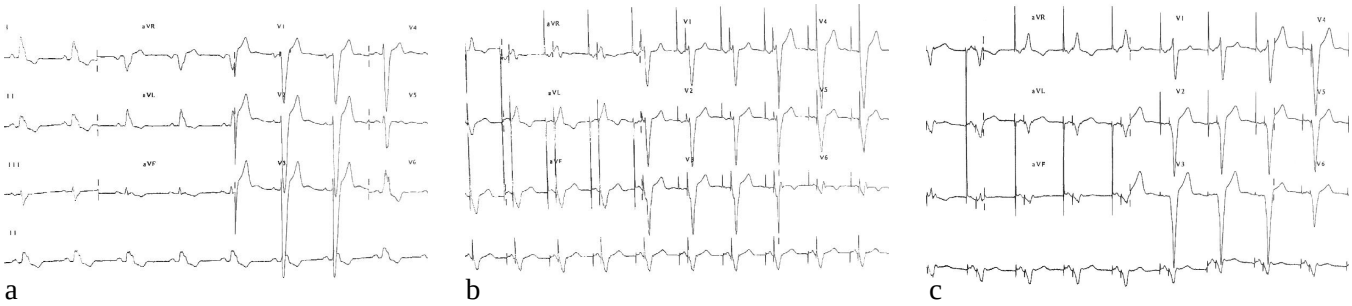


Figure 2. NYHA-functional class in the four patients before pacemaker implantation and at 1 month and 6 months after implantation.



a b c

Figure 3. ECG recordings before implantation (panel a), during right ventricular DDD pacing (panel b) and during biventricular DDD pacing (panel c), in the patient from Figure 1.

Conclusion

Our initial experience in four patients with CHF caused by dilated cardiomyopathy suggests that the patients undergoing heart resynchronization therapy in combination with the closed-loop sensor controlled by the autonomic nervous system benefit in terms of a clear improvement in the NYHA-functional class, a physical exercise capacity, and in physiological responses to variations in heart rate. The arterial pressure during exercise was improved with this therapeutic modality.

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