Reverse ventricular remodeling and improved functional capacity after ventricular resynchronization in advanced heart failure

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Key words:
Cardiac resynchronization therapy; Cardiopulmonary stress test; Echocardiography; Heart failure.

Background. **Ventricular resynchronization is a non-pharmacological treatment for advanced heart failure refractory to drug therapy and with intraventricular conduction delay. We describe the time course of echocardiographic and functional recovery after resynchronization in 31 patients (mean age 67 ± 8 years).**

Methods. **We evaluated NYHA class, echocardiogram, respiratory function, and cardiopulmonary test before pacemaker implantation (baseline), after 1-3 months (short-term evaluation), and 10-15 months afterwards (long-term evaluation, n = 21 patients). Mortality at 1 year was considered.**

Results. **Both at short and long term, patients improved NYHA class, ventricular function, and ventricular volumes. Already at short term, we observed an increase in oxygen consumption at peak exercise (12.6 ± 0.6 vs 10.5 ± 0.5 ml/kg/min), oxygen consumption at anaerobic threshold (9.8 ± 0.6 vs 8.3 ± 0.6 ml/kg/min) and oxygen pulse (8.3 ± 0.5 vs 7.5 ± 0.5 ml/beat). Ventilatory efficacy (VE/VCO_2 slope) and alveolo-capillary diffusion (estimated by the measurement of lung diffusion capacity for carbon monoxide - DLCO) improved only at long term (VE/VCO_2: 40.7 ± 1.6 vs 45.3 ± 1.8; DLCO: 70.3 ± 2.7 vs 59.4 ± 5.9% of predicted, p = 0.05). The 1-year mortality was 9.7%.**

Conclusions. **Ventricular resynchronization is linked to a fast and prolonged recovery of NYHA class, echocardiographic variables and stress tolerance. The improvement of indexes known to carry a prognostic value confirms that ventricular resynchronization can positively interfere with the evolution of the disease.**

(Ital Heart J 2005; 6 (7): 578-583)

Received November 22, 2004; revision received February 22, 2005; accepted February 24, 2005.

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Introduction

The natural history of heart failure has dramatically changed in the last decade due to the availability of drugs that improved its prognosis – i.e. vasodilators, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, spironolactone[1-4]. However, the course of the disease is still fatally progressive[1,5], so that the quest for non-pharmacological approaches other than transplantation is altogether active. The observation that a delay in atrioventricular and intraventricular conduction may contribute to pump dysfunction[6,7] led to the development of cardiac resynchronization therapy. Following early disappointing results of the short PR stimulation technique[8], the currently used biventricular stimulation is a promising tool: an improvement in clinical and instrumental variables and a reduced mortality have been shown in most studies on patients in advanced NYHA class, sinus rhythm, QRS > 150 ms[9-15].

Cardiopulmonary stress test and Doppler echocardiography are widely used in the serial, non-invasive evaluation of patients with heart failure, because they have a good prognostic value and may be used both to tailor medical treatment and to enlist patients for transplantation[16-19]. Cardiopulmonary evaluation is, in fact, of pivotal relevance. Oxygen consumption at peak exercise (pVO_2) is a strong predictor for short- and long-term mortality, being a continuous variable in clinical stratification[19-21]. A negative prognostic significance is also carried on by abnormal values of the slope in the ventilation/carbon dioxide production (VE/VCO_2) ratio[20,22,23], by a low oxygen pulse (pO_2)[24], by a poor diffusion capacity for carbon monoxide (DLCO)[25,26].

The aim of the present study was to characterize the time course of changes in clinical, echocardiographic and cardiopulmonary variables in patients with heart failure who underwent ventricular resynchronization.

Methods

Population. We studied 31 patients (24 males and 7 females, mean age 67 ± 8 years) with severe heart failure and intraventricular conduction delay, undergoing atrio-biventricular pacemaker implantation at our Institution since 2001. Patients' characteristics are summarized in table I. The investigation reported conforms to the principles outlined in the declaration of Helsinki (1964). Etiology of heart failure was ischemic in 13 patients (42%), idiopathic in 16 (52%), alcoholic in 1 case (3%), and valvular in 1 case (3%). NYHA class was 3.1 ± 0.1 (NYHA class II 4/31, 13%; NYHA class III 19/31, 61%; NYHA class IV 8/31, 26%). Therapy was tailored in all patients complying with the international guidelines, with appropriate doses of diuretics and the highest tolerated doses of ACE-inhibitors, angiotensin II type 2 inhibitors, beta-blockers and spironolactone. Incidentally, the severity of heart failure did not allow to reach target doses in most patients: in detail, beta-blockers were often not introduced due to hypotension, bradycardia or advanced atrioventricular block. In fact, the follow-up protocol allowed for adjustments in the dose of diuretics and beta-blockers after implantation.

Protocol. The evaluation of NYHA class, Doppler echocardiography, respiratory function and cardiopulmonary stress test was performed before pacemaker implantation (baseline evaluation), 1-3 months later (short-term evaluation) and 12-15 months later (long-term evaluation). So far, the latter is available for 21 patients. Of the remaining 10, 3 died before the programmed follow-up, and 7 were alive but did not perform the on-site visit for personal or logistic reasons (in this case, a telephone follow-up with evaluation of the NYHA class is available). Therefore, the 1-year mortality was considered 9.7% (i.e. 3 patients).

Table I. Clinical characteristics of the patients.

Sex (M/F)	24 (77%)/7 (23%)
Ischemic cardiomyopathy	13 (42%)
Non-ischemic cardiomyopathy	16 (52%)
Alcoholic cardiomyopathy	1 (3%)
Valvular cardiomyopathy	1 (3%)
NYHA class	
II	4 (13%)
III	19 (61%)
IV	8 (26%)
ACE-inhibitors	26 (84%)
AT-2 inhibitors	5 (16%)
Beta-blockers	16 (52%)
Diuretics	28 (90%)
Spironolactone	16 (52%)
Digitalis	12 (39%)

ACE = angiotensin-converting enzyme; AT-2 = angiotensin II type 2.

Echocardiography. For each test, we evaluated: left ventricular end-diastolic and end-systolic volumes, left ventricular ejection fraction (ejection fraction as percent of end-diastolic volume), and stroke volume. The extent of mitral regurgitation was defined in four grades (minimal, mild, moderate, severe) as assessed at color Doppler analysis.

Cardiopulmonary stress test. Patients were studied with a Sensor Medics 2900 Pulmonary Function Test System (Sensor Medics Inc., Yorba Linda, CA, USA). A preliminary test of pulmonary function measured 1) the forced vital capacity, 2) the forced expiratory volume in 1 s (FEV_1), and DLCO (single expiration test). Variables were expressed as percentages of the theoretical values, predicted according to age, sex and body mass. Stress test was performed on a bicycle ergometer with a ramp protocol of 10 W every min preceded by a 2-min warm-up period. The equipment allowed the beat-to-beat evaluation of: 1) oxygen consumption (VO_2), 2) VCO_2, 3) VE, 4) tidal volume, and 5) respiratory rate. The ECG was monitored by a Marquette Case16 recorder (Marquette Inc., Milwaukee, WI, USA) and blood pressure was measured by a sphygmomanometer. The respiratory quotient was calculated averaging 20 s. The anaerobic threshold was measured with the V-slope method. pVO_2 was defined as the highest VO_2 obtained during any test phase (usually it corresponded to the highest workload reached), and was corrected for body weight (i.e. ml/kg/min). Submaximal exercise capacity was evaluated as the VO_2 at the anaerobic threshold (VO_2AT), while the degree of ventilatory efficacy was considered as the VE/VCO_2 ratio during exercise; this ratio (i.e., VE/VCO_2 slope) increases linearly during exercise. Finally, pO_2 was calculated as the ratio between VO_2 and heart rate: pO_2 corresponds to the product between stroke volume and artero-venous oxygen difference, and can be used as an index of stroke volume itself when peripheral oxygen extraction is normal[27].

Pacemaker implantation. After sedation (midazolam 5-10 mg), patients underwent pacemaker implantation with a programmable V-V interval. Catheters (Capsure Model 5334 and Attain Model 2187; Medtronic Inc., Minneapolis, MN, USA) were positioned in the right atrium, right ventricular apex, posterolateral or lateral veins in the left ventricle. We avoided the anterior site, due to the poor results of stimulation from this approach[9].

Statistical analysis. Data are reported as mean ± 1 SD. ANOVA for repeated measurements was used to compare data at baseline vs short and long term. To compare therapy, prevalence of mitral regurgitation and other dichotomous variables, we used the χ^2 test. A p value of ≤ 0.05 was considered as statistically significant.

Results

Short- and long-term results regarding echocardiographic and cardiopulmonary parameters are shown in tables II-IV and in figures 1-3.

Functional class. At short term (3.3 ± 1.1 months from implantation) the NYHA class showed a significant improvement (2.2 ± 0.1 vs 3.1 ± 0.1, $p < 0.0001$). The improvement persisted also in the surviving patients at long term (1.9 ± 0.3 vs 3.1 ± 0.2, $p = 0.0001$; 21 patients performed also the whole follow-up examination).

Therapy. Three months after resynchronization, patients tolerated a higher dose of carvedilol (15.9 ± 3.2 vs 10.9 ± 2.6 mg/die, $p < 0.01$). At long term, we maintained the same drug regimen (20.5 ± 3.4 mg/die, compared to 8.7 ± 2.3 mg/die at baseline and 14.4 ± 3.1 mg/die at short term, $p < 0.05$). The doses of the remaining drugs were kept unchanged.

Electrocardiography. The presence of left bundle branch block with a QRS duration ≥ 150 ms was among the inclusion criteria in these patients: indeed, QRS was 160 ± 6 ms before implantation. Already at short term after resynchronization, there was a significant reduction in QRS duration (to 130 ± 5 ms, $p < 0.01$) that persisted at long term in the 21 patients studied (129 ± 7 ms, $p < 0.01$ vs 160 ± 6 ms baseline) (Table II). We could not find any relationship between the degree of QRS narrowing and the amount of improvement in either echocardiographic or cardiopulmonary variables (e.g. ejection fraction, volumes, pVO_2, pO_2).

Echocardiography. Table II shows the improvement in the echocardiographic parameters. Left ventricular ejection fraction increased significantly at short term, with a further improvement in the long term. A similar behavior was observed in left ventricular end-diastolic diameters and volumes, which were progressively reduced over time. The prevalence of patients showing a moderate-to-severe mitral regurgitation (due to a distorted mitral annulus) was high at baseline and significantly reduced at short and long term as well (Fig. 1). The echocardiographic stroke volume did not change over time.

Respiratory function. The effect of resynchronization on respiratory function is shown in table III. No changes in vital capacity or in FEV_1 were observed. On the other hand, diffusion capacity estimated with DLCO improved at long term, with a greater effect in patients showing a more severe abnormality at baseline (Fig. 2).

Table III. Effects of biventricular stimulation on lung function.

	Baseline (n=31)	Short term (n=31)	Long term (n=21)
FVC (% theoretical)	87 ± 3	92 ± 3	93 ± 4
FEV_1 (% theoretical)	81 ± 4	85 ± 3	88 ± 2
DLCO (% theoretical)	59 ± 6,	64 ± 3	70 ± 3*

DLCO = diffusion capacity for carbon monoxide; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s. * $p < 0.05$ vs baseline (n = 31).

Table IV. Effects of biventricular stimulation on cardiopulmonary stress test.

	Baseline (n=31)	Short term (n=31)	Long term (n=21)
Peak heart rate	107 ± 3	110 ± 6	108 ± 5
pVO_2 (ml/kg/min)	10.5 ± 0.5	12.6 ± 0.6*	12.9 ± 0.7*
VO_2AT (ml/kg/min)	8.3 ± 0.6	9.8 ± 0.6*	10.1 ± 0.7*
pO_2 (ml/beat)	7.5 ± 0.5	8.3 ± 0.5*	9.1 ± 0.7*
VE/VCO_2	45.3 ± 1.8	42.3 ± 1.2	40.7 ± 1.6*

pO_2 = oxygen pulse; pVO_2 = oxygen consumption at peak exercise; VE/VCO_2 = ventilation/carbon dioxide production ratio; VO_2AT = oxygen consumption at the anaerobic threshold. * $p < 0.05$ vs baseline.

Table II. Effects of biventricular stimulation on ECG and echocardiography.

	Baseline (n=31)	Short term (n=31)	Long term (n=21)
Resting heart rate (b/min)	88 ± 11	72 ± 9*§	69 ± 11*°§
QRS duration (ms)	160 ± 6	130 ± 5*	129 ± 7*
Systolic blood pressure (mmHg)	105 ± 9	110 ± 8	111 ± 11
Ejection fraction (%)	24.5 ± 1.4	27.8 ± 1.5*	35.5 ± 2.1*°
LVEDD (mm)	74 ± 12	65 ± 9*	59 ± 8*°
LVEDV (ml)	249 ± 18	207 ± 15*	157 ± 15*°
Severe mitral regurgitation	26/31 (84%)	13/31 (41%)*	7/21 (33%)*
Stroke volume (ml)	53 ± 4	56 ± 5	54 ± 4

LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume. * $p < 0.05$ vs baseline (n = 31); ° $p < 0.05$ vs baseline and short term (n = 21); § some patients became pacemaker-dependent for sometime after implant.

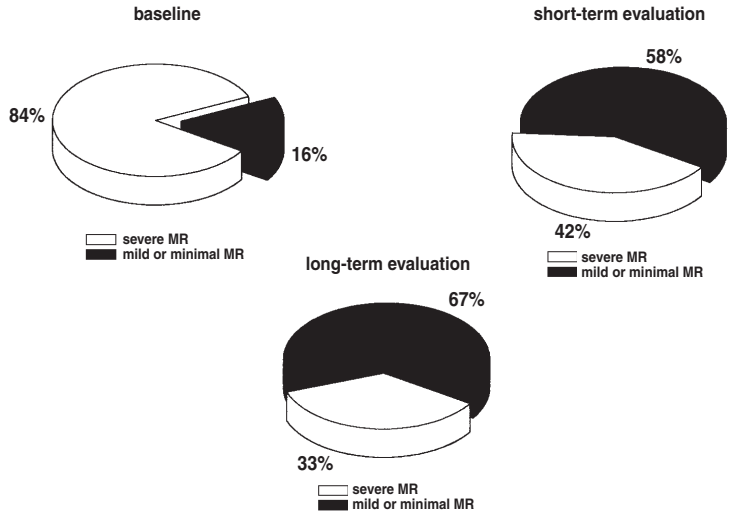

Figure 1. *Mitral regurgitation (MR) after resynchronization.* Upper left panel, *baseline: 84% of patients (24 of 31 patients) had severe MR.* Upper right panel, *short term: the prevalence of severe MR dropped to 42% (18 patients).* Lower panel, *long term: among 21 patients studied, severe MR was observed only in 7 (33%). This change in prevalence over time was significant.*

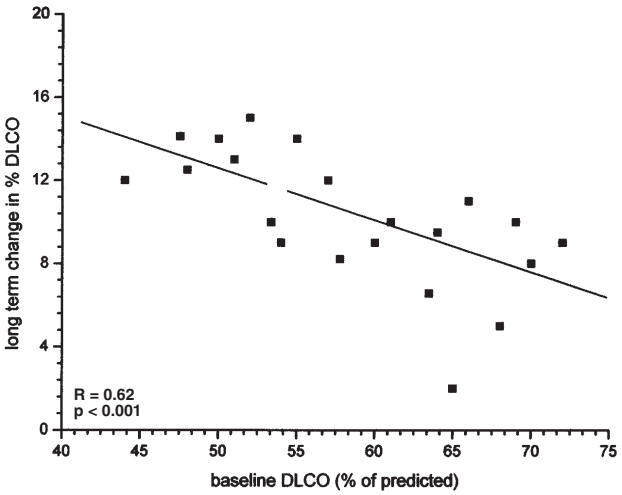

Figure 2. *Relationship between baseline diffusion capacity for carbon monoxide (DLCO) (expressed as percentage of the theoretical value) and its percent increase at long term. Data for the 21 patients at long-term follow-up are shown: a trend toward a greater recovery in more severely compromised patients is evident.*

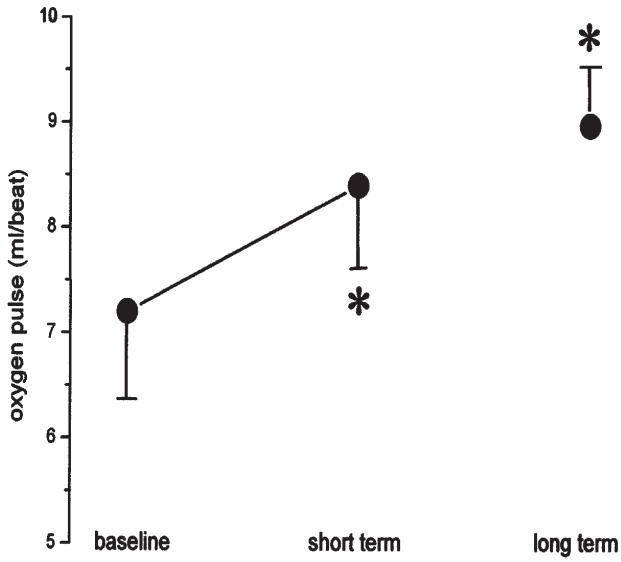

Figure 3. *Gradual increase in oxygen pulse over time in patients, hinting to an improvement of antegrade stroke volume.*

Cardiopulmonary stress test. Table IV shows the influence of resynchronization on the performance during cardiopulmonary stress test. Maximal heart rate was unchanged both at short and long term. pVO_2 improved by 20% already at short term, and remained higher at long term; a similar trend was observed with anaerobic threshold. pO_2 improved by 11 and 18% ($p < 0.05$) at short and long term respectively (Fig. 3). Finally, VE/VCO_2 slope was reduced significantly at long term (by 11%, $p < 0.05$).

Responders versus non-responders patients: mortality. If we consider as responders all patients who improved ≥ 1 NYHA class[28] and increased pVO_2 by at least 10%, we have 58% responders at short term (18/31 patients). At long term, overall responders were 13/21 (61%); 2 patients who had been responders at short term became non-responders (we found that this was due to poor capture of the ventricular lead), while none of the initial non-responders became responder. Thus, while technical problems may hinder the favorable effects seen at short term, an initial unfavorable response to resynchronization seems to predict a negative long-term outcome: indeed, 3 patients who died of progressive heart failure (9.7%) had all been classified as non-responders at the short-term evaluation. Among the variables taken into account at baseline, we could not define any clinical, electrocardiographic, echocardiographic or cardiopulmonary parameter that could identify responders from non-responders to resynchronization.

Discussion

Our study shows that, after ventricular resynchronization, patients with moderate to severe heart failure significantly improved NYHA class, exercise capacity and ventilatory efficiency, and underwent a progressive reverse ventricular remodeling. These potentially favorable changes occurred quite rapidly, and were maintained at the yearly follow-up.

Resynchronization and functional capacity. Various studies demonstrated that ventricular resynchronization improves exercise tolerance[10,12]. In a retrospective analysis of 50 patients, Auricchio et al.[29] showed an increase in pVO_2, VO_2AT and VE/VCO_2 slope after 3 months from implantation, the highest benefit being present in patients having a baseline pVO_2 < 75th percentile. Besides confirming that observation, our data demonstrate a long-term persistence of the improvement in pVO_2, VO_2AT and VE/VCO_2 slope. Of note, exercise performance at baseline was significantly worse in our patients than in the report by Auricchio et al. (where baseline pVO_2 was slightly less than 16 ml/kg/min); thus, even sicker patients received a relevant benefit from ventricular resynchronization.

Several pathophysiological mechanisms lie behind the observed improvement in functional capacity: they need to be verified through appropriate experimental studies, however some speculations may be worthwhile. In contrast to previous data showing only an increase in ventricular ejection fraction 1 year after implantation[27] and similarly to what has recently been reported by multicenter studies[10,12,13], we observed a reduction in ventricular diameters and volumes, that is, a reverse ventricular remodeling. The time course of this remodeling is such that the first variable to improve is the left ventricular end-diastolic volume, while ejection fraction shows a later improvement. Despite the improvement in ventricular ejection fraction, stroke volume was unchanged in patients after resynchronization: however, we should consider that the stroke volume assessed by the Simpson's equation does not account for the regurgitant volume. In fact, the correction in functional mitral regurgitation (with the attendant decrease in the regurgitant volume) was associated with a significantly higher pO_2, pointing *de facto* to an increase in the aortic, effective stroke volume. Also the long-term improvement in the ventilatory response may derive from a reduction in venous pulmonary pressure, secondary to a better mitral valve function.

Resynchronization and the heart-lung complex. Ventilation and diffusion capacity of the alveolo-capillary membrane were enhanced, albeit not returning to normal, on a long-term basis 1 year after implantation: this indicates a limited remodeling of pulmonary abnormalities. The reduced alveolo-capillary diffusion is partly due to interstitial edema, and partly to interstitial collagen deposition and fibrosis: whereas interstitial edema might have been slowly reabsorbed following the sustained reduction in left ventricular end-diastolic pressure, interstitial fibrosis was clearly irreversible. The improvement in DLCO was greater in sicker patients, hinting to a coexistence of interstitial edema and permanent fibrosis, despite high doses of diuretics.

Can the improved functional parameters modify the prognosis? Most cardiopulmonary parameters have been used to improve prognostic stratification in advanced heart failure. In our practice, we utilize two criteria to identify patients at high risk for subsequent mortality. The first is that introduced by Mancini et al.[18] in 1991 that defines a patient at high risk when his/her pVO_2 is < 14 ml/kg/min. The second criterion has been proposed in 2002 by Gitt et al.[20], and combines VO_2AT (< 11 ml/kg/min) and VE/VCO_2 slope (> 34) as risk indexes. According to the first classification, before resynchronization 84% of patients were at high risk; at short and long term, they decreased at 65 and 53% respectively. Considering Gitt's criteria, 84% of patients were at high risk at baseline; at short and long term, the percentage decreased at 66 and 60% respectively. In other words, about 19% of our patients moved to a better risk class. In fact, pVO_2, VO_2AT, VE/VCO_2 are all continuous prognostic indexes: cut-offs are only of practical value. Following this reasoning, one may imply that *any* improvement in *any* of the cardiopulmonary parameters has an inherent favorable prognostic significance. Indeed, the 1-year mortality was 9.7%, similar to that reported by Mascioli et al.[27], and to that of patients in NYHA class II (5-15%)[2,3].

A final consideration regards non-responder patients. Interestingly, in our patients we could foresee an unfavorable prognosis already at short term; on the other hand, a worsening of the clinical picture in the long term was due, in this group of patients, to technical reasons that we could deal with. So far, no criteria have been identified to understand who will benefit from ventricular resynchronization; indeed, no differences were seen before implantation in any of the clinical and instrumental variables examined in our patients. Site of stimulation is very important, the left lateral wall being the most effective[9]: for this reason, we avoided pacing from the anterior wall. Promising information on the likelihood of response to pacing may arise from tissue Doppler analysis[28], but we were not routinely using it in the present study.

In conclusion, our data confirm that ventricular resynchronization improves the prognostic indexes and the functional capacity in patients with advanced heart failure. However, many treatments were effective in the acute phase and did not reduce mortality[30]. Only randomized controlled studies will demonstrate if ventricular resynchronization leads to a prolonged survival, and will indicate which patients could benefit from this intervention.

Acknowledgments

We are grateful to the staff of the Electrophysiology Laboratory (Valeria Gius, Giovanni Stellacci RN) for their help in the procedures, and to the colleagues of the Cardiology Department for their support in the care and follow-up of the patients.

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