

ORIGINAL ARTICLES

ARRHYTHMIAS

Antitachycardia Pacing Efficacy Significantly Improves With Cardiac Resynchronization Therapy

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Introduction and objectives. The effect of cardiac resynchronization therapy on antitachycardia pacing still has to be determined.

Patients and method. A total of 490 heart failure patients with an indication for an implantable cardioverter-defibrillator participated in the VENTAK CHF/CONTAK CD study, a single-blind, randomized, placebo-controlled study. We compared antitachycardia pacing efficacy in patients with or without cardiac resynchronization therapy. Due to the device design, antitachycardia pacing was always given simultaneously via both left and right leads (i.e., biventricular antitachycardia pacing). Patients were randomized at the time of implantation, with the pacing mode being programmed accordingly one month later.

Results. During follow-up, 32 patients received antitachycardia pacing: 15 with cardiac resynchronization therapy and 17 without. In the 15 patients receiving resynchronization, 221 episodes of tachycardia were treated by antitachycardia pacing. The sinus rhythm conversion rate was 90.5%. In patients not receiving resynchronization, there were 139 episodes of tachycardia and the sinus rhythm conversion rate was 69.1%. The sinus rhythm conversion rate in the cardiac resynchronization therapy group was significantly higher than that in the control group ($P < .0001$). Moreover, antitachycardia pacing efficacy improved with time in the whole study population.

Conclusions. The efficacy of biventricular antitachycardia pacing in heart failure patients is significantly better in those with cardiac resynchronization therapy than in those without.

Key words: Cardiac resynchronization therapy. Antitachycardia pacing. Implantable defibrillator.

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La eficacia de la estimulación antitaquicardia mejora tras la terapia de resincronización cardíaca

Introducción y objetivos. No se conoce el efecto de la terapia de resincronización cardíaca en el tratamiento de la estimulación antitaquicardia.

Pacientes y método. En el Estudio VENTAK CHF/CONTAK CD han participado 490 pacientes con insuficiencia cardíaca e indicación para desfibrilador implantable. Se trata de un estudio aleatorizado, simple ciego y controlado con placebo. Hemos comparado la eficacia de la estimulación antitaquicardia en pacientes con o sin terapia de resincronización. La estimulación antitaquicardia fue administrada simultáneamente desde ambos electrodos, izquierdo y derecho, debido al diseño del dispositivo empleado. La aleatorización se realizó en el momento del implante, y se programó el modo de estimulación, según el grupo asignado, un mes después.

Resultados. Un total de 32 pacientes recibió terapias de estimulación antitaquicardia (15 con terapia de resincronización y 17 sin terapia de resincronización) durante el período de seguimiento del estudio. Entre los 15 pacientes tratados con resincronización se registraron 221 terapias, con una tasa de reversión a ritmo sinusal del 90,5%. En el grupo no asignado a terapia de resincronización se registraron 139 terapias, con una tasa de reversión a ritmo sinusal del 69,1%. La tasa de reversión en el grupo asignado a resincronización fue significativamente mayor que la del grupo control ($p < 0,0001$). El beneficio de la estimulación antitaquicardia se incrementó con el tiempo para toda la población del estudio.

Conclusiones. La eficacia de la estimulación antitaquicardia biventricular en pacientes con insuficiencia cardíaca fue significativamente mejor en los pacientes con terapia de resincronización cardíaca respecto de los que no la recibieron.

Palabras clave: Terapia de resincronización cardíaca. Estimulación antitaquicardia. Desfibrilador implantable.

ABBREVIATIONS

RA: right atrium.
 ICD: implantable automatic defibrillator.
 ATP: antitachycardia pacing.
 EF: ejection fraction.
 ACE inhibitors: angiotensin converting enzyme inhibitors.
 NYHA: New York Heart Association.
 CRT: cardiac resynchronization therapy.
 VT: ventricular tachycardia.
 LV: left ventricle.
 RV: right ventricle.

INTRODUCTION

The use of implantable automatic defibrillators (ICD) with antitachycardia pacing (ATP) therapies has been demonstrated to reduce the number of discharges from the device.¹⁻³ The efficacy of ATP ranges from 80% to 94%⁴⁻¹² and can be affected by factors such as baseline cardiopathy, presence of necrosis due to previous infarctions, left ventricle (LV) size, and to some extent sympathetic tone prior to tachycardia.^{5,6,11,13}

The appearance of ventricular resynchronization therapy and the opportunity for multiple site and cardiac chamber stimulation opens up a wide range of alternatives for ATP. We should first evaluate the influence of site of stimulation on ventricular tachycardia suppression by ATP. In patients with heart failure and substantial LV dilatation, single site ATP on the right side can be less effective than expected. Cardiac resynchronization therapy (CRT) enables us to apply these treatments from the LV wall or simultaneously from both ventricles. A previous study reports biventricular pacing proved more effective at suppressing ventricular arrhythmias than isolated apical right ventricular (RV) pacing.¹⁴

Cardiac resynchronization therapy can contribute to ATP efficacy through positive ventricular remodeling by reducing stress on the wall and facilitating ATP which, perhaps, reduces the recurrence of ventricular tachycardia (VT).¹⁵⁻¹⁷ However, the usefulness of CRT in reducing recurrent ventricular arrhythmias over time has not been definitively established¹⁸ and appropriate prospective studies should be designed to determine this.

The objective of this study is to investigate the influence of resynchronization therapy on ATP efficacy in suppressing VT episodes by comparing ATP efficacy in a group of patients with CRT versus another group without.

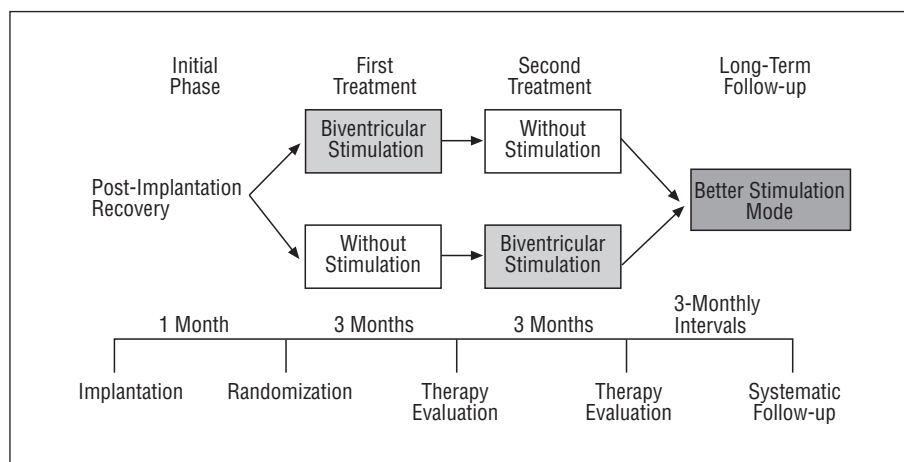
PATIENTS AND METHOD

Study Design

The VENTAK CHF/CONTAK CD study had a 2-phase design¹⁹⁻²² and both parts were used for the ATP arrhythmia suppression efficacy substudy. The original design appears in Figure 1. We enrolled patients presenting symptomatic heart failure (New York Heart Association [NYHA] class III-IV); indicated for ICD following guidelines of the American College of Cardiology; with ejection fraction (EF) <35%; QRS complex >120 ms; and optimized medical treatment for 1 year. We excluded patients indicated for pacemaker implantation for bradycardia. All participants gave written informed consent and the study was approved by the trial committees of each participating institution.

Patients included in the first phase received an ICD (VENTAK CHF/CONTAK CD, Guidant Corporation) with conventional electrodes for the right atrium (RA) and RV. Left ventricular pacing was initially achieved through epicardial placement via left thoracotomy. This was later replaced by intravenous placement of an electrode with stimulation and sensing functions

Figure 1. Initial VENTAK CHF/ CONTAK CD study design. Randomization is prior to implantation. After a 1-month recovery period, devices are randomly programmed to biventricular pacing (BiV) or VVI at 40 beats/minute to avoid stimulation. After 3 months follow-up, patients change mode of stimulation and follow-up continues for another 3 months.



(EASYTRAK, Guidant Corporation) through the coronary sinus. At 30 days post-implantation, devices were programmed appropriately in each therapy group.

Half the patients were randomized to biventricular pacing in VDD mode and half to VVI at 40 beats/minute to avoid stimulation. At 3 months, therapies were reversed. After a second 3-month follow-up phase, further programming changes were made at the discretion of the researcher.

In 1999, the study design was modified to permit stabilization of the therapy groups (Figure 2). The cross-sectional design was replaced by 2 independent therapy groups: 1 with biventricular pacing and the other without stimulation for a period of 6 months.

Antitachycardia Pacing Efficacy Substudy

We enrolled patients from both phases of the principal study. From the first phase we included VT episodes occurring during the first 3 month follow-up; for patients included in the second phase, we analyzed episodes occurring over the first 6 months (Figure 3). The objective of the substudy was to analyze ATP therapy efficacy with and without CRT.

We enrolled 490 patients with heart failure and indication for ICD in the ATP substudy: half (245 patients) with CRT and half without. Baseline cardiomyopathies among these patients were ischemic heart disease (69%) and nonischemic dilated cardiomyopathy (31%). Mean EF was $22.3 \pm 7.9\%$. We found 33% were in NYHA functional class II, 58% in class III and 9% in class IV. We excluded NYHA class I patients.

We recorded previous monomorphic VT at implantation in 45% of patients, nonsustained VT in 26%, polymorphic VT in 13%, and ventricular fibrillation in 13%. Wide QRS complex was caused by left bundle branch block in 54% of patients and right bundle branch block in 13%. We found non-specific anomalies of intraventricular conduction in 33%.

Angiotensin enzyme conversion (ACE) inhibitors or angiotensin receptor blockers (ARA-II) were being administered to 87% of patients, diuretics 85%, digoxin 68%, and beta-blockers 47%.

From this population we selected 32 patients receiving ATP therapies (15 with CRT, 17 without CRT) because of VT episodes during the study period. To evaluate ATP efficacy, we analyzed all VT episodes stored in device memories of patients who received ATP therapy at least once.

Materials

Initially, LV stimulation was from an epicardial electrode, implanted via left thoracotomy, with LV lateral wall implantation as our first option. We first used the VENTAK CHF ICD, which permits simulta-

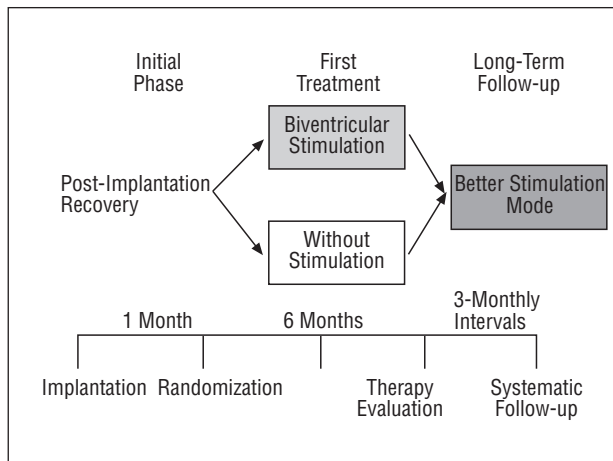


Figure 2. Initial design modification. At the request of the Food and Drug Administration the initial cross-sectional design was modified and a parallel design was adopted with a 6 month follow-up. BiV indicates biventricular.

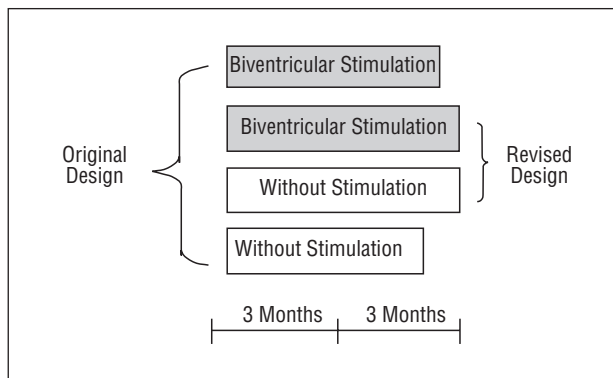


Figure 3. Our study included patients during the first period of randomization, so half have a 3 month follow-up and the other half a 6 month follow-up. BiV indicates biventricular.

neous stimulation in both ventricles with the epicardial electrode and a standard defibrillation electrode (EN-DOTAK, Guidant). Later, we deployed an endocardial electrode in the coronary sinus, implanted for stimulation and sensing in the LV. This electrode is passed through the coronary venous system over a guidewire. Left and right ventricular electrodes are connected in parallel so that stimulation and sensing are simultaneous. This parallel arrangement means ATP is administered from both electrodes. Consequently, ATP therapies were biventricular in all patients, independently of the final programming assigned.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation (SD). The proportion of successful

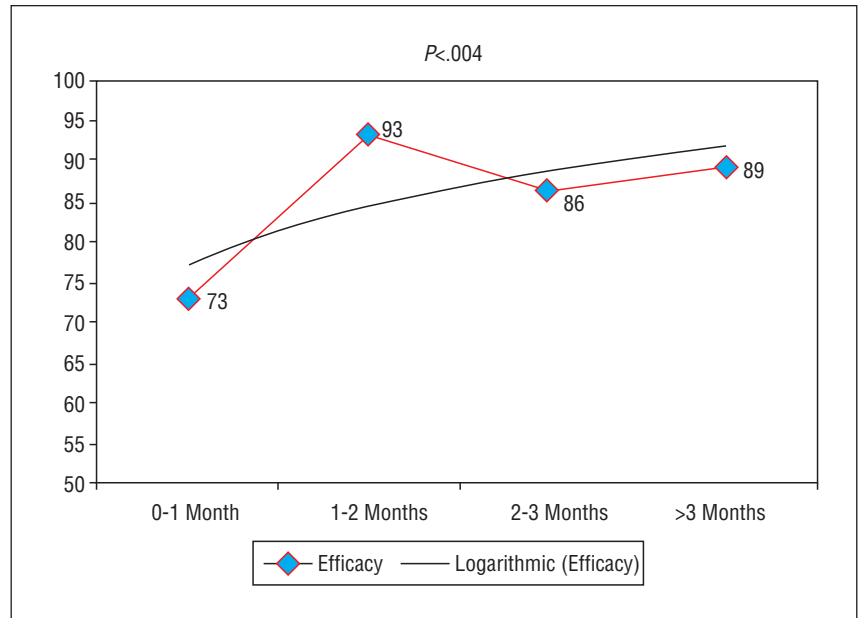


Figure 4. Global antitachycardia pacing efficacy. Efficacy is 73% in the first month and increases significantly during the study.

monomorphic VT conversions over time was analyzed with the Mantel-Haenszel test. Conversion rates at specific times in the 2 groups were compared with the Fisher exact test. Values of $P \leq .05$ were considered statistically significant.

RESULTS

Of 490 patients, 32 received ATP therapies: 15 in the group with CRT and 17 in the group without. All ATP episodes were stored in the device memory permitting observation of intracavity electrograms to evaluate therapy efficacy. In the first month, global ATP therapy efficacy was 73%, rising to 93% in the second month, 86% in the third and 89% in patients with >3 month follow-up. These data show a significant increase in long-term ATP efficacy ($P < .004$) (Figure 4).

In patients with CRT, we recorded 221 episodes of ventricular arrhythmias treated with ATP, with a conversion rate of 90.5%. In the group without CRT we recorded 139 episodes of ATP, with only 69.1% efficacy ($P < .001$) (Table 1).

Some patients in both groups presented episodes of arrhythmic storms during follow-up. Consequently, many episodes were concentrated in a small number of patients which may constitute a bias when evaluating

the results. To minimize this, in the final results we repeated the analysis excluding all patients presenting >30 episodes: 3 with CRT and 1 without CRT. The result was less striking but still statistically significant ($P < .004$) with a higher conversion rate among patients with CRT (Table 1).

We also evaluated ATP efficacy as a function of electrode site. We found 51% of leads were implanted in the lateral wall, 29% in the anterior wall, 14% in a posterior vein, and 5% in the apex. We found no electrode sites in the middle cardiac vein or coronary sinus. Table 2 shows ATP efficacy at 6 months in the CRT group as a function of electrode position. We found a trend towards higher ATP therapy conversion rates in lateral versus anterior wall sites. This probably reflects the greater hemodynamic benefit of lateral wall stimulation.^{23,24} Analysis of ATP efficacy in the lateral vein showed it was greater in the with CRT group when compared with lateral implantation in the without CRT group suggesting efficacy may be more closely related with the effect of ventricular remodeling than with the ATP administration site. However, due to the limited number of episodes recorded in both groups we did not find statistically significant differences.

We do not provide data on posterior wall sites due to the very limited number of patients in this group.

TABLE 1. Differences in Antitachycardia Pacing Efficacy Between the 2 Groups

Treatment Group	Total Number of Episodes	Efficacy $P < .0001$	Total Number of Episodes Excluded >30	Efficacy $P < .004$
Resynchronization 0-6 months	221	90.5%	57 (12 patients)	93%
Baseline 0-6 months	139	69.1%	75 (16 patients)	83%

DISCUSSION

Our study shows ATP efficacy is greater in patients with CRT and that it tends to improve over time.

Moreover, the effectiveness of this biventricular treatment is comparable to that described in previous reports, when it is only applied from the RV apex.⁴⁻¹²

Previous studies have shown biventricular pacing can reduce the inducibility of ventricular arrhythmias,¹⁷ ventricular extrasystoles,¹⁶ or incidence of spontaneous ventricular arrhythmias¹⁵. Higgins et al¹⁵ analyzed the first patients included in the VENTAK CHF study and found episodes of tachycardia treated in 13 of 32 patients (41%). Five patients (16%) had 1 episode during biventricular pacing while 11 (34%) presented an event in the non-stimulation phase. Three patients (9%) received therapies in both phases. The difference between the number of patients needing therapy in the 2 groups was statistically significant ($P<.0035$). In a group of 20 patients, Walker et al¹⁶ showed that biventricular pacing reduced the number of ventricular extrasystoles over time by comparison with patients in sinus rhythm and RV apical stimulation. Zagrodzky et al¹⁷ showed a reduction in the inducibility of significant arrhythmias with biventricular pacing by comparison with RV pacing. However, the efficacy of biventricular pacing in the long-term reduction of arrhythmias has yet to be determined.

The InSync ICD study¹⁴ showed that ATP therapies in biventricular mode could be more effective than those administered from RV apex only. The study recorded 472 episodes of VT or fast ventricular tachycardia in 26 patients; 339 episodes in 17 patients in the VT zone, 107 episodes in 8 patients in the fast VT and 26 in 8 patients in the fast VT zone. Biventricular pacing with ATP was more effective in the VT and fast VT zones ($P<.001$).

Due to the device design employed, all ATP therapies in our study were applied simultaneously from both ventricles. Consequently, conversion rate efficacy in both groups can only be explained by the mid- and long-term effects of resynchronization on myocardial function. Various mechanisms may be involved: first, hemodynamic improvement in patients treated with CRT.²⁵⁻²⁷ Many studies have shown lower incidence of ventricular arrhythmias in patients with compensated heart failure.²⁸⁻³⁰ Moreover, biventricular pacing permits simultaneous activation of large areas of myocardium, permitting earlier, homogeneous repolarization. In these conditions ventricular extrasystoles are unlikely to find areas of functional block that facilitate reentry. Third, homogenization of refractory ventricular periods obtained via biventricular pacing. Finally, CRT would diminish sympathetic tone in patients with ventricular dysfunction³¹⁻³³ and create a potent antiarrhythmic effect.³³

TABLE 2. Efficacy as a Function of Electrode Site

Lateral wall	44%	
Anterior wall	37%	
Posterior wall	19%	
Site	Resynchronization Efficacy	Episodes
Anterior	85%	4
Lateral	96%	9
Site	Resynchronization Efficacy	Baseline Efficacy
Lateral	96%	81%

Ideally, we would have long-term results although we can hypothesize that 3-6 month data are representative of long-term effects. Unpublished data from the Incidencia study confirm the effect of anatomic and electric remodeling in an early post-implantation phase. More interesting data would illustrate long-term ATP efficacy in patients without CRT due to worsening of their conditions over time. Data from this study are insufficient as the longest follow-up was only 6 months and in most patients randomized to the baseline group CRT was activated at the end of follow-up.

Antitachycardia Pacing Efficacy According to Electrode Site

Conversion efficacy is greater in lateral than anterior wall sites. Initially, 2 factors may contribute to this phenomenon: the importance of electrode site at the moment of biventricular ATP and remodeling due to LV biventricular pacing. We found that not only are lateral sites better than anterior sites in the CRT group but they are also better in the group without CRT. This indicates that the mechanism underlying efficacy is more closely related to ventricular remodeling than the final site of ATP administration. This is consistent with other studies^{23, 24} that show hemodynamic improvement is greater with LV stimulation from a lateral site by comparison with anterior stimulation.

CONCLUSIONS

Our results indicate that ATP therapy efficacy, when administered in both ventricles, is as high as in previous studies^{4-12,34} and that it improves during follow-up. There is a great difference between patients with cardiac resynchronization therapy and those without, with a trend that indicates efficacy is highly dependent on site of electrode stimulation and that the lateral site is the best option. All this probably reflects the effect of positive secondary myocardial remodeling on cardiac resynchronization.

Limitations

Our study presents some limitations. The first is the low number of episodes of VT treated with ATP during the follow-up. From 490 patients, we only selected 32 (6.5%). This has 2 explanations: the short follow-up period and the fact that device programming was optional. Unfortunately, many devices did not have ATP therapies activated. The final result is that the number of patients included is reduced, which somewhat undermines the soundness of the results.

Another limitation is the fact that we are dealing with a sub-group study, which means results should be analyzed with care.

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