

Antiarrhythmic Effect of Cardiac Resynchronization

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Cardiac resynchronization therapy (CRT) has proved efficient in improving symptoms and quality of life and reducing cardiovascular mortality. However, research into possible antiarrhythmic effects of the therapy per se is extremely limited. When evaluating response to CRT, we find patients who, despite good functional evolution, present ventricular tachycardia or sudden death. Consequently, response to CRT tends to be evaluated as a combined criterion encompassing functional improvement and mortality.¹⁻³ However, some data indicate functional improvement is accompanied by reduced risk of sudden death. For instance, the CARE study⁴ showed reduced cardiovascular mortality in the group of patients treated with CRT. Analysis of the data reveals this reduction pertained to mortality due to refractory heart failure and sudden death. Furthermore, several studies with small patient numbers show a reduction in the number of arrhythmic episodes, ventricular extrasystole and inducibility of ventricular arrhythmias.⁵⁻¹¹ Although left ventricle stimulation can produce arrhythmogenesis in specific patients, this is very rare.

Hypothetically, the reduction in sudden death obtained with CRT could limit the need for defibrillator implantation in primary prevention in patients indicated for resynchronization and without sustained ventricular arrhythmias, as it substantially reduces the probability of severe ventricular arrhythmias. However, data that substantiate this hypothesis have yet to be published although there are numerous observations of patients implanted with resynchronization pacemakers without defibrillators, who die presenting ventricular tachycardia.

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The beneficial effect of CRT in arrhythmia is produced by many different mechanisms. Although the pathophysiology has not been researched in depth, some reports suggest the existence of CRT-derived mechanisms that may reduce the incidence of severe ventricular arrhythmias.

A first pathophysiologic mechanism is related to the reversed cardiac remodeling observed in CRT.^{9,10} Reversed remodeling means lower wall stress and, therefore, less tension on myocardial fibers. This could lead to decreased triggered activity or modification of possible reentry circuits. Walker et al⁵ showed biventricular stimulation reduced the number of extrasystoles and nonsustained ventricular tachycardia in a cohort of patients with advanced heart failure. Although the group of patients was small, the differences were significant. More recently, Kies et al⁸ observed a significant reduction in inducibility of ventricular tachycardia in a group of 18 patients who had survived an episode of sudden death, presented advanced heart failure and undergone pacemaker implantations. Notably, the reduced inducibility was in patients who presented inverse remodeling at 6-month follow-up and was therefore directly associated with structural improvement. Structural changes may modify electrophysiologic properties of tissue, avoiding the presence of regions with conduction delay and potential reentry circuits.

Another possible antiarrhythmic effect is due to hemodynamic improvement and the consequent reduction of sympathetic tone. Increased sympathetic tone is clearly linked to greater arrhythmogenesis through multiple mechanisms (triggered activity, shorter refractory periods, etc).

On the other hand, the fact that CRT reduces sympathetic activity through hemodynamic improvement has been reported elsewhere.¹¹ This improvement permits the use of beta-blockers that prior to CRT were not tolerated by the patient. Beta-blockers are well known to have an antiarrhythmic effect and significantly reduce total mortality and sudden death in patients with heart failure.¹²

Finally, stimulation in both ventricles can associate with electrophysiologic effects that entail reduced presence of arrhythmias as well as more effective anti-tachycardia therapy. In a study of patients with previous infarction and reduced ejection fraction who were referred for electrophysiologic study, Zagrodzky et al⁷ found less inducibility of arrhythmias. They found greater reduction in inducibility of sustained ventricular tachycardia with simultaneous biventricular pacing than with RV pacing.

The purely preventive electrophysiologic effect of inducibility is probably linked to reduced dispersion of refractoriness because in simultaneous biventricular pacing, depolarization and repolarization occur within a shorter space of time. This reduces the margin for stimulus reentry through regions with conduction delay.

In Spain, the multicenter INCIDENCIA study is investigating whether biventricular stimulation reduces the incidence of ventricular arrhythmias. When data are published, we will have additional information from a randomized study specifically designed to focus on this topic.

In this issue of *REVISTA ESPAÑOLA DE CARDIOLOGÍA*, Fernández-Lozano et al¹³ emphasize the greater efficacy of antitachycardia pacing in patients with biventricular stimulation. They enrolled patients indicated for CRT with defibrillator implantations and initially employed a cross-sectional design that was later modified to a design with 2 independent therapy groups. The authors found that antitachycardia pacing resulted in more efficient reestablishment of sinus rhythm in patients being resynchronized with simultaneous biventricular pacing. Antitachycardia pacing was 90% efficient in patients with CRT and 69% in patients without CRT. These significant differences were maintained even when patients with >30 episodes were excluded to avoid introducing a bias in the results because they accounted for a very high percentage of episodes. Even when data refer to a very small subgroup of patients in the VENTAK CHF/CONTAK CD study, this observation is very interesting and permits us to continue analyzing the antiarrhythmic effect of CRT. Fernández-Lozano et al¹³ report that benefits are probably due to a remodeling effect and change in sympathetic tone after CRT, given that both groups were treated with simultaneous biventricular antitachycardia pacing. Bocchiardo et al¹⁴ analyzed the effectiveness of antitachycardia pacing and found no differences when comparing patients with biventricular automatic implantable defibrillators (ICD) with patients with conventional ICDs. However, these populations were not clinically comparable so data reported by Bocchiardo et al do not contradict Fernández-Lozano et al¹³ but underline the greater effectiveness of biventricular antitachycardia pacing in patients with resynchronizing ICDs.

From a defibrillator design standpoint, it is important to assess the need to provide biventricular antitachycardia pacing. A priori it seems more likely that antitachycardia therapy by simultaneous biventricular overstimulation would be more effective than right ventricular pacing alone. From a mechanistic point of view, pacing at a site closer to the region of delayed conduction of the circuit allows better penetration of the stimulus in the tachycardia circuit and its termination. The initial Guidant cross-sectional design included in this study administered antitachycardia therapy and stimulation simultaneously in both ventricles through a single pacemaker lead but current devices have independent leads for both ventricles. This improves programming alternatives (independent adjustment of right and left thresholds, capacity for sequential activation of ventricles, avoiding double sensing). However, this advance is again accompanied by delivery of antitachycardia pacing from the right ventricle electrode only. Thus, the possible beneficial effect of biventricular antitachycardia pacing is not being used in most current devices. New studies are needed to compare the efficacy of delivering right ventricular antitachycardia pacing with biventricular delivery.

Cardiac resynchronization therapy has an antiarrhythmic effect through a range of mechanisms. Studies with greater patient numbers would be welcome as they might determine the magnitude of this beneficial effect, which would have repercussions on the evaluation of suitability for ICD or resynchronizing pacemaker implantation. On the other hand, it is important to analyze the best way to deliver antitachycardia therapy, to achieve the greatest efficacy possible.

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