

Cardiac Resynchronization Therapy: When the Pacing Site Really Matters

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Cardiac resynchronization therapy has been one of the major qualitative advances made in the treatment of heart failure in recent decades, and it strongly underlines the relationship between heart mechanics, hemodynamic function, and electrophysiology. Since the 1980s a number of clinical and experimental studies have shown that abnormalities in intraventricular conduction, associated or not with delays in atrioventricular conduction, can adversely affect hemodynamic performance through the discoordination of cardiac contraction.¹ Over the last 20 years, researchers (especially in Europe) have explored the extraordinarily simple yet original hypothesis that mechanical discoordination caused by delays in electrical conduction can be reverted by atrioventricular electrical stimulation. This should improve the hemodynamics of the failing heart in patients with refractory heart failure, left ventricular dysfunction, and intraventricular conduction abnormalities.^{2,3} The first clinical studies, which were initially designed to determine the mechanism of action of this technique, showed that in the latter subgroup of patients electrical stimulation of the left ventricle corrected intraventricular dyssynchrony, improved the values of acute hemodynamic variables, increased systolic efficiency, and optimized diastolic function without increasing the heart rate or the consumption of oxygen by the myocardium.^{4,5} Later, large scale clinical trials gradually showed that cardiac resynchronization therapy was safe, that a percutaneous approach was technically possible, that it improved patients' functional status and quality of life, that it reduced the number of hospitalizations, and that it inversely remodeled the left ventricle—a powerful prognostic predictor of heart failure.⁶⁻⁸ The inverse remodeling achieved was found to be similar in its magnitude to that obtained with beta-adrenergic blockers,⁸ and that it was associated with a

reduction in ventricular myocardial fibrosis.^{9,10} More recently, two large, multicenter trials—COMPANION¹¹ and CARE-HF¹²—have demonstrated the positive effect of resynchronization therapy on long-term total mortality in this same subgroup of patients.

These beneficial clinical effects have been consistently proven in a number of randomized, controlled clinical trials involving a population of over 4000 patients with homogeneous clinical characteristics, and follow up times of more than a year.^{6,7,11,12} This solid evidence has been progressively introduced into the clinical guidelines of the main scientific societies on both sides of the Atlantic. Since 2005 both European and American clinical guidelines have referred to cardiac resynchronization therapy as a class I indication with a level of evidence A for the treatment of patients with refractory heart failure of any etiology and with a New York Heart Association functional class of III or IV, left ventricular dysfunction, and signs of dyssynchrony (commonly detected as an increase in the width of the QRS complex).¹³

Although much has been learned in recent years, and this treatment has become ever more widely used,¹⁴ resynchronization therapy is still associated with a number of unanswered questions and limitations. In this issue of the *Revista Española de Cardiología*¹⁵ one of these problems is investigated: the technical difficulty of implanting a lead that, after being inserted percutaneously via the coronary venous system, must stimulate the epicardium of the lateral region of the left ventricle. Arbelo et al,¹⁵ who have enjoyed great success in their use of cardiac resynchronization therapy, describe how a simple maneuver (developed for other reasons for use in the coronary arterial system) aids the advance of over-the-wire leads through the chosen venous branch in patients with complicated venous anatomy.

The interest this study awakens is double. Firstly, it highlights one of the main problems of cardiac resynchronization therapy: the existence of patients who fail to improve or who only improve slightly. Lack of response, which is complex and probably multifactorial in origin,¹⁶ is seen in some 20%-30% of patients, and should be well understood so that this sophisticated treatment is offered only to patients with the best chance

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of responding adequately. However, it may be that (at least in some cases) the lack of a positive effect can be traced back to the very act of implantation: not every lead implanted via the coronary sinus for the stimulation of the left ventricle may offer a reasonable chance of achieving resynchronization, and therefore of obtaining significant clinical benefit.

In part owed to the classic work led by Josephson,¹⁷ it is now known that in a large percentage of patients with left bundle block the areas of most delayed electrical activation are those in the lateral region of the left ventricle. This finding is more consistent in patients with idiopathic dilated cardiomyopathy since the relative integrity of the distal His-Purkinje system generally favors a more predictable electrical activation pattern with the most delayed areas in the lateral and basal regions of the left ventricle. In patients with left bundle block and ventricular dysfunction of ischemic etiology, in whom the distal conduction system is usually more affected by the presence of areas of necrosis, the endocardial activation patterns are much more variable and less predictable.¹⁷ However, although some studies have described a good correlation between left bundle block and the mechanical desynchronization variables obtained by tissue Doppler analysis, and between the former and the delay in the electrical activation of the free wall of the left ventricle,¹⁸ the correlation between local electrical activation and the resulting contraction is still a matter of debate and is yet to be properly studied in such patients. For example, in ventricles with extensive infarctions, the areas with the greatest electrical delay usually coincide with areas of scar tissue with little capacity for functional recovery despite their being electrically excitable. Recent data show that the presence of transmural scarring in the lateral region detected by magnetic resonance favors the absence of a clinical response to resynchronization therapy, despite there being echocardiographic signs of dyssynchrony.¹⁹ This correlation between the presence of scar tissue and the lack of a positive response is even greater in the absence of myocardial viability.²⁰ It has not been shown in patients with transmural scarring that electrical stimulation in another region of the left ventricle can provide any clinical benefit.

From a clinical point of view, there is evidence to suggest that systematically implanting the left ventricular lead in the lateral region (or close by) is clinically more beneficial than implanting in the anterior region; such inferences have been drawn from acute hemodynamic studies⁵ and by evaluating resynchronization with tissue Doppler techniques.²¹ In the most powerful study, Rossillo et al²² compared the clinical efficacy and mortality associated with cardiac resynchronization in 233 patients with respect to the final position of the lead in the left ventricle. These authors described the most consistent improvements in functional capacity and left ventricular function to be obtained in patients

in whom implantation had been performed in the lateral region. However, some of these patients were not randomized, and the stimulation points were therefore chosen on the basis of their accessibility. This limited the possibility of distinguishing the effects of the lead position from those of the factors that might have impeded implantation in the lateral position. Further, in a small observational study,²³ no differences were seen in the clinical progress of patients implanted in the lateral or other positions.

Given the partly contradictory information available, the question arises as to where the best point for stimulating the left ventricle might lie. Clearly, the idea that *all* patients obtain the greatest benefit from implanting the lead in the lateral region is too simplistic. This concept will probably be revised in the next few years, especially for patients with cardiomyopathies of ischemic origin and with non-viable scar tissue in the lateral region. No-one can doubt that, at least theoretically, the most attractive strategy would be to define the non-viable areas of the myocardium and to determine in each patient the boundaries of the area where mechanical activation is most delayed; its electrical pre-excitation could lead to a greater resynchronization capacity. However, no prospective studies have been performed to validate this strategy, and despite the questions raised in the literature, it would appear reasonable to make the effort to systematically implant the lead in the lateral region of the left ventricle (either directly via the marginal venous branches or via their collateral branches). One should not fall into the temptation of stimulating from the great cardiac vein or from other excessively anterior positions (which would be easier from a technical point of view), at least as a first option and without an electromechanical argument for supporting such a decision. The work of Arbelo et al¹⁵ highlights the need to select and reach the area that needs to be stimulated, and not allow the implantation position to be conditioned by anatomical difficulties that should be overcome by good technique and patience.

Further, the technical maneuver described by Arbelo et al highlights why, from the outset (the implantation technique), this new therapy should be considered multidisciplinary. Medical professionals from different fields of cardiology are involved in the selection, follow-up and optimization of the devices implanted and the treatment of patients in whom resynchronization is performed. The implantation procedure involves different cardiac stimulation teams, and the idiosyncrasy of the technique itself—which requires a certain degree of surgical ability, the confident use of catheters, guidewires, electrophysiological, and hemodynamic material, and experience in the implantation of defibrillators, etc.—clearly reflects the therapy's multidisciplinary nature. Indeed, the technique for implanting resynchronization therapy devices straddles conventional cardiac stimulation,

electrophysiology, hemodynamics and heart surgery. All these disciplines provide important technical resources, and close collaboration between those who practice in these areas is often essential for overcoming the logical limitations of each. This collaboration becomes vital when trying to maintain a high quality resynchronization program.

At some centers, a single section with a certain degree of experience in all these disciplines can keep an excellent resynchronization program afloat. However, not all centers have personnel with such experience, and any absence of collaboration is likely to result in difficulties in a procedure that, while demanding, should not be seen as extraordinary in the current day and age. The need for a multidisciplinary approach has been understood by several international scientific societies, and there have been suggestions made that specific resynchronization therapy education and training programs be developed. Ideally these would include specialized training in heart failure and arrhythmology.²⁴

Finally, Arbelo et al¹⁵ report an excellent success rate (over 95% for all implants attempted). Through the proper use of the instruments designed for performing implantations (especially catheters designed to selectively cannulate the venous branches), by the choice of good equipment (including good x-ray equipment), by possessing the will to climb the learning curve, and over time and with patience, this figure is not beyond the reach of references centers that perform a large number of implantations every year.

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