



## EDITORIAL COMMENT

# Triple-site pacing for cardiac resynchronization in atrial fibrillation – an opening onto different scenarios<sup>☆</sup>



## *Pacing multi-site para ressincronização cardíaca na fibrilhação auricular – uma janela com cenários diferentes*

Mário Oliveira<sup>a,b</sup>

<sup>a</sup> Laboratório de Pacing e Eletrofisiologia, Serviço de Cardiologia, Hospital de Santa Marta, Carnaxide, Portugal

<sup>b</sup> Instituto de Fisiologia, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

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Cardiac resynchronization therapy (CRT), whether or not combined with an implantable cardioverter-defibrillator, is one of the most important innovations in the treatment of chronic heart failure (CHF). It is able to restore ventricular synchrony in patients with severe intraventricular conduction disturbances, particularly complete left bundle branch block or QRS interval >150 ms. These conduction disorders, found in a third of cases of severe CHF, lead to mechanical dyssynchrony and systolic dysfunction, and several large multicenter randomized trials have demonstrated that CRT improves functional class and quality of life and significantly reduces mortality and hospitalizations for CHF. This treatment modality is increasingly studied and used in clinical practice, with ever-growing numbers of

specialists and reference centers, and, most importantly, with many thousands of patients treated successfully worldwide.<sup>1,2</sup>

Despite the consistently positive results of electromechanical resynchronization, including improvements in hemodynamic parameters and increased cardiac output, reverse remodeling and in a significant number of cases normalization of systolic function and left ventricular (LV) volumes, several important questions remain to be answered. One is how to improve the response rate to CRT (even when selected in accordance with the international guidelines, up to 30% of patients do not respond). Another is the question of the best pacing configuration (biventricular or multi-site). A third issue is how to improve CRT response in patients with CHF and atrial fibrillation (AF), who account for over 20% of individuals in the European cardiac resynchronization therapy survey, and for whom CRT is a class IIa recommendation, level of evidence B, since CRT is less beneficial in these patients.<sup>1</sup> Patients with AF undergoing CRT are generally older and have more comorbidities, lower response rates

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E-mail address: [m.martinsoliveira@gmail.com](mailto:m.martinsoliveira@gmail.com)

and higher overall mortality compared with those in sinus rhythm.<sup>1,3</sup>

The article by Marques et al.<sup>4</sup> published in this issue of the *Journal* compares different LV pacing configurations in patients with permanent AF, QRS >120 ms (not necessarily with criteria for complete left bundle branch block) and ejection fraction (EF) <40% who had a CRT device implanted. In a single assessment up to one month after implantation, the authors determined the impact in the acute post-implantation phase of different pacing configurations on cardiac output (analyzed by invasive arterial pressure measurement), QRS duration and EF (calculated by echocardiography). They suggest that triple-site ventricular pacing (Tri-V) (right ventricular [RV] apex and right ventricular outflow tract [RVOT] plus left ventricle) produces better results in all three parameters than conventional biventricular (Bi-V) pacing (RV apex or RVOT plus left ventricle).

This was not a study of clinical response rate or reverse remodeling during follow-up, but an analysis of the behavior of different variables in the acute phase (up to one month post implantation) that compared different configurations after 15 minutes of stable pacing. Its focus on patients with permanent AF makes the study more interesting, since other studies have shown less benefit in this patient group. Tri-V pacing has been studied by other authors, although all in relatively small samples and none exclusively of AF patients. In a 2012 study with 43 patients, Rogers et al. showed that Tri-V pacing was associated with better clinical and echocardiographic results than Bi-V pacing in 12-month follow-up.<sup>5</sup> All the study population had EF <35% and QRS duration  $\geq$ 150 ms but only 14% had AF. The 20 patients treated by Tri-V pacing with RV, high RV septum and LV leads had no better echocardiographic results than the Bi-V pacing group. In a comparison study of 21 patients in sinus rhythm (New York Heart Association class III or IV, EF <35% and QRS >120 ms), Yoshida et al., like Marques et al., showed that in the acute phase, Tri-V pacing (RV apex and RVOT plus LV) leads to significant QRS shortening and improvements in LV dP/dt, cardiac output, ventricular synchrony on echocardiography and EF, compared to Bi-V pacing.<sup>6</sup>

The possibility of more options in multi-site pacing configurations may help improve resynchronization therapy by producing a pattern of ventricular activation that is closer to physiological depolarization, not only through more pacing sites, but also by enabling optimization of VV interval programming according to the type of mechanical dyssynchrony observed. In the study by Marques et al., it would have been interesting to have analyzed dyssynchrony by the different types of echocardiography available (septal flash or apical transverse motion, tissue synchronization imaging, tissue Doppler imaging, radial strain, and three-dimensional), in order to provide some objective correlation between the observed hemodynamic benefits and the degree of ventricular dyssynchrony. For example, when the LV lead was connected to the atrial channel, left pacing was always 25–40 ms earlier, while if the RVOT lead was connected to the atrial channel pacing was always earlier at this site. This possible limitation, which results from the impossibility of simultaneous triple-site pacing, could be tested in a detailed study of dyssynchrony.

At a time of growing interest in multi-site and multi-point pacing for the treatment of CHF, there have still been few studies on dual-site RV pacing with LV pacing. Thus, the article by Marques et al. points to a viable alternative that is safe (with no increase in procedural or fluoroscopy times) and potentially beneficial in an important subgroup of CHF patients. Although the study population was small, it is also interesting to note that the results for the different parameters for Bi-V pacing with the lead in apical position or in the RVOT were similar. Other ways in which this study differs from the experience of other groups include the lower percentage of patients with ischemic cardiomyopathy (25%), the number who required atrioventricular node ablation (6/40, 15%) and, as pointed out by the authors, the equipment used to measure cardiac output (the Flo-Trac III™ Vigileo™ monitoring system, Edwards Lifesciences, Irvine, CA, USA), which has not been evaluated in this context.

The need for viable solutions to the problem of non-responders to CRT is reason to pursue triple-site pacing, which has the potential to improve patterns of electromechanical activation and thus ventricular performance. Future studies will be necessary to determine if this modality brings benefits to all patients ('one size fits all'), or whether selection of the best Tri-V configuration should be individualized according to the type of dyssynchrony identified. The TRIUMPH-CRT trial, designed to compare optimized Tri-V pacing (based on the left pre-ejection interval, measured during implantation) with standard Bi-V pacing in patients with severe systolic dysfunction and QRS >150 ms, without criteria for complete left bundle branch block, will provide valuable information on this important subject.

The relationship between electrocardiographic, hemodynamic and echocardiographic findings in the acute phase and sustained clinical benefit will need to be demonstrated in randomized trials with larger populations and long-term follow-up. In this context, Marques et al.'s study is a valid contribution to the search for viable options in the non-pharmacological treatment of CHF.

## Conflicts of interest

The author has no conflicts of interest to declare.

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