

EDITORIAL COMMENT

Triventricular Pacing

A Nice Concept to Be Proven*



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Cardiac resynchronization therapy (CRT) is now a well-recognized therapy in chronic heart failure patients on optimal medications with depressed left ventricular (LV) function and a wide QRS. This electrical therapy has shown significant benefit on morbidity and mortality endpoints, functional capacity, and LV remodeling in large randomized trials (1). If the majority of patients are responders to CRT with different magnitudes, a substantial percentage of patients are nonresponders, 30% to 50% according the criteria that define a response to CRT. CRT is delivered with simultaneous or sequential biventricular pacing with 1 right ventricular (RV) and 1 LV lead, and with a right atrial lead in patients with sinus rhythm (1). To decrease the rate of nonresponders, pacing the ventricles in 3 sites (either 2 in the RV and 1 in the LV or 2 in the LV and 1 in the RV), rather than 2 sites (1 in the RV and 1 in the LV), has been proposed. This is called triple-site pacing or triventricular pacing. The physiological rationale for triple-site pacing is based on different factors (2).

First, in patients with left bundle branch block, 2 different patterns of LV activation have been described with electroanatomic mapping: type I activation with slow propagation and type II with a U-shaped activation resulting from a line of functional block. Type II activation is associated with more responders to conventional CRT, whereas type I is associated with a higher percentage of nonresponder

patients with the hypothesis that LV pacing in only 1 spot is not sufficient to correct LV dyssynchrony (2).

Second, the presence and the location of myocardial scar and the position of the LV lead with respect to these regions play an important role. Implantation of an LV lead in an area of a myocardial scar may be associated with slow conduction and block (2).

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In this issue of *JACC: Clinical Electrophysiology*, Providencia et al. (3) report the long-term potential benefit of triple-site pacing on long-term survival compared with conventional biventricular pacing using a single-center propensity score matched cohort study with 34 patients in each arm. The triple-site was achieved with 2 LV leads and 1 RV lead in 15 patients and 2 RV leads and 1 LV lead in 19 patients. The conclusion, a significant reduction of 56% for all-cause mortality and heart transplantation, has to be interpreted very cautiously. The statistics are occasionally confusing if only the results are considered. How should we conclude the benefit of one therapy over another on morbidity and mortality with only 34 patients in each arm? Interestingly, the rate of ventricular arrhythmias requiring appropriate therapies was decreased significantly by triple-site pacing and, more important, the addition of a second RV or LV lead was not associated with a higher rate of complications. Finally, the response to CRT was not different between the triple-site pacing with the addition of a right or a LV lead (3).

The concept of triple-site pacing is interesting, but one of the limitations is that this pacing modality has been evaluated only in small studies with soft endpoints. The addition of a second RV lead showed modest hemodynamic improvement in an acute hemodynamic study including only 21 patients with an increase in cardiac output, LV maximum dP/dt, and in LV end-systolic volume and ejection fraction

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(4). A small randomized trial including 66 patients comparing conventional biventricular pacing and triple-site pacing over a 12-month follow-up showed a significant increase in LV ejection fraction with triple-site pacing without any clinical benefit (5).

For triple-site pacing with 2 LV leads, we have data from modest studies. Two acute hemodynamic studies reported controversial results (6,7). The feasibility of the implantation of 2 LV leads has been shown, with a 85% to 95% success rate (8,9).

The clinical benefit of triple-site pacing with 2 LV leads needs to be demonstrated definitively. We cannot conclude today that this pacing modality is superior to conventional pacing. In our own randomized study, with a modest population of 42 patients, we did not show any clinical benefit of triple-site pacing over biventricular pacing and showed only a modest but significant improvement in LV ejection fraction and LV end-systolic volume (8). Lenarczyk et al. (10), in a randomized trial including only 98 patients, showed a benefit of triple-site pacing only on New York Heart Association functional class and 6-min walk test compared with biventricular pacing. Rogers et al. (11), in a double-blind randomized crossover trial, compared triple-site pacing with biventricular pacing. Two groups were identified: group A with 2 RV leads and 1 LV lead and group B with 2 RV leads and 1 LV lead. The primary endpoint at 3 months of follow-up was the 6-min walk test, with a significant increase in the 2 groups in favor of multisite pacing.

The additive value of the study reported by Providencia et al. (3) is the follow-up duration, with a median time of 6 years; however, this strength is

counterbalanced by the small population size, which can generate speculation but not strong evidence. One important point is the impact on the battery longevity, with a reduction in the triple-site group of about 6 to 7 months. The same findings are reported with multisite pacing, a different concept providing LV bifocal stimulation but in the same vein. Finally, by adding a second LV lead in the coronary sinus, the fear of a proarrhythmic effects was not observed, as demonstrated the findings reported by Ogano et al. (12). In fact, triple-site pacing was associated with a reduction of ventricular arrhythmias requiring appropriate therapies.

The concept of triple-site pacing was also tested in the nonresponder in the V3 trial. There were no benefits with respect to clinical and echocardiographic endpoints, but a high rate of severe advanced events (10%) after the implantation of a second LV lead was observed (13).

So the concept of triple-site pacing is attractive to try to further improve the response to CRT by improving LV synchrony. However, we do need solid and strong data to support the benefit of triple-site pacing. The rate of complications and 2 LV pacing delivery have to be addressed in large trials, as does the impact of decreased battery longevity. Three clinical trials are ongoing to assess the impact of triple-site pacing with either 2 RV leads or 2 LV leads.

... Wait and see....

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REFERENCES

1. Daubert JC, Saxon L, Adamson PB, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. *Europace* 2012;14:1236-86.
2. Rinaldi CA, Burri H, Thibault B, et al. A review of multisite pacing to achieve cardiac resynchronization therapy. *Europace* 2015;17:7-17.
3. Providencia R, Rogers D, Papageorgiou N, et al. Long-term results of triventricular versus biventricular pacing in heart failure: a propensity-matched comparison. *J Am Coll Cardiol EP* 2016; 2:825-35.
4. Yoshida K, Seo Y, Yamasaki H, et al. Effect of triangle ventricular pacing on haemodynamics and dyssynchrony in patients with advanced heart failure: a comparison study with conventional biventricular pacing therapy. *Eur Heart J* 2007;28: 2610-9.
5. Anselme F, Bordachar P, Pasquié JL, et al. Safety, feasibility, and outcome results of cardiac resynchronization with triple-site ventricular stimulation compared to conventional cardiac resynchronization. *Heart Rhythm* 2016;13:183-9.
6. Pappone C, Rosanio S, Oreto G, et al. Cardiac pacing in heart failure patients with left bundle branch block: impact of pacing site for optimizing left ventricular resynchronization. *Ital Heart J* 2000;1:464-9.
7. Padeletti L, Colella A, Michelucci A, et al. Dual site left ventricular cardiac resynchronization therapy. *Am J Cardiol* 2008;102:1687-92.
8. Leclercq C, Gadler F, Kranig W, et al. A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. *J Am Coll Cardiol* 2008; 51:1455-62.
9. Lenarczyk R, Kowalski O, Kukulski T, et al. Triple-site biventricular pacing in patients undergoing cardiac resynchronization therapy: a feasibility study. *Europace* 2007;9:762-7.
10. Lenarczyk R, Kowalski O, Kukulski T, et al. Mid-term outcomes of triple-site vs. conventional cardiac resynchronization therapy: a preliminary study. *Int J Cardiol* 2009;133:87-94.
11. Rogers DP, Lambiasi PD, Lowe MD, Chow AW. A randomized double-blind crossover trial of triventricular versus biventricular pacing in heart failure. *Eur J Heart Fail* 2012;14: 495-505.
12. Ogano M, Iwasaki YK, Tanabe J, et al. Antiarrhythmic effect of cardiac resynchronization therapy with triple-site biventricular stimulation. *Europace* 2013;15:1491-8.
13. Bordachar P, Alonso C, Anselme F, et al. Addition of a second LV pacing site in CRT nonresponders rationale and design of the multicenter randomized V(3) trial. *J Card Fail* 2010;16:709-13.

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