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EDITORIAL COMMENT

Cardiac Resynchronization Therapy

The More Pacing Sites, the Better the Outcome?*

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Cardiac resynchronization therapy (CRT) by biventricular pacing has been established as a nonpharmacologic therapy for patients with drug-refractory heart failure and ventricular conduction delay (1). A good proportion of patients treated with CRT show significant amelioration of their symptoms and functional capacity, reversal of the maladaptive remodeling process, and prolongation in life expectancy. The proportion of nonresponders (estimated at about 40%) is likely to be reduced by better selection (such as the presence and magnitude of mechanical dyssynchrony and scar burden), optimization of therapy application (tuning of atrioventricular and interventricular delay), and choosing

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the best pacing site. The most common left ventricular (LV) pacing site selected for delivering CRT is the free lateral wall, but the question is whether adding more pacing sites could improve outcome. Indeed, it seems feasible that placement of multiple pacing leads at different ventricular sites would create multiple waves of electrical activation, thus further reducing asynchrony in case of ventricular conduction delay. A few recent observational studies in heart failure patients have attempted simultaneous pacing at 2 sites within the same LV region, a few case reports appeared about pacing at 2 different sites within the LV, and some studies have evaluated 2 simultaneous pacing sites within the right ventricle (RV) along with 1 LV pacing site. Although the results of these small, single-center, observational studies showed a large individual variability, triple ventricular pacing sites, no matter whether RV or LV, resulted in a larger hemodynamic improvement compared with conventional biventricular pacing.

The TRIP-HF (Triple Resynchronization In Paced Heart Failure Patients) study presented in this issue of the *Journal* (2) is the first randomized, prospective multicenter trial comparing a triple-site stimulation—2 epicardial transvenous leads placed on the anterior and lateral or posterolateral LV wall and 1 RV lead—with conventional biventricular pacing. The TRIP-HF study enrolled a highly selected yet small group of patients with severe heart failure presenting with a slow ventricular rate during atrial fibrillation (AF). Leclercq et al. (2) showed that compared with dual-site biventricular pacing, triple-site ventricular stimulation promoted further LV reverse remodeling as assessed by LV end-systolic and -diastolic volumes and ejection fraction, at 3-month follow-up. The results of this study are of great interest, and the investigators should be congratulated for having tested this important pathophysiological concept. However, there are a few more considerations and some caveats that should be considered before widely applying triple-site stimulation in larger groups of patients.

The primary echocardiographic objective of the study, the quality of ventricular resynchronization, as defined as the Z ratio, was missed. The Z ratio is calculated simply from the duration of the ejection and filling times with respect to the overall cardiac cycle and is an index of global mechanical dyssynchrony in heart failure patients (3). It is one of the many echocardiographic indexes recently proposed for evaluating mechanical dyssynchrony (4). In the TRIP-HF study, the Z ratio was unchanged after CRT compared with baseline; moreover, the Z ratio did not significantly change between the 2 different stimulation modes. Although these results may seem paradoxical in light of publications on the relevance of mechanical dyssynchrony (4), recent publications from prospective multicenter trials show that several echocardiographic indexes of mechanical dyssynchrony do not predict response to CRT or even change after CRT (5,6). Thus, the results of the TRIP-HF study are not surprising and support the idea that broad applicability of a single echocardiographic parameter in daily practice is still not feasible.

The main secondary end point of the TRIP-HF study was a change in LV end-systolic volume during dual- and triple-site stimulation. Both end-systolic and -diastolic volumes were reduced more during triple-site stimulation compared with dual-site stimulation. As a result, the mean LV ejection fraction increased more during triple-site (+9 percentage points) than during dual-site stimulation (+3 percentage points) compared with baseline. The absolute mean increase of the LV ejection fraction during dual-site stimulation was unusually modest for this group of patients. Indeed, patients with AF included in other CRT studies using conventional biventricular pacing had similar mean

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baseline volumes and LV ejection fraction, but at comparable follow-up times showed an increase of LV ejection fraction ranging between +6 and +12 percentage points (7–9). An explanation for these and other results may reside in the inclusion criteria of the TRIP-HF study. After all, 50% of the study population consisted of patients with RV pacing, whereas the other 50% had a de novo implant and was without the requirement of a wide QRS complex. Indeed, QRS duration varied widely (SD = 47 ms at a mean value of 167 ms), implying that several patients with initially narrow QRS complexes were also included. In such patients, conventional biventricular pacing may actually not improve LV function (6), or even worse, cardiac mechanics (10). Furthermore, although a 3-month run-in period was used, in de novo implanted patients some of the effects may have been caused by rate regularization. In patients with poor cardiac function rate regularization, even using RV pacing has beneficial effect in patients with AF and His bundle ablation (11). Therefore, although the study addressed better application of CRT, the other prerequisite for the largest beneficial effect of CRT (patient selection) might have been less carefully handled. The fact that the TRIP-HF study was performed in patients with a slow ventricular rate during AF in need of antibradycardia pacing implies that the benefits of triple-ventricular stimulation can be related to better ventricular resynchronization without being possibly confounded by changes in atrioventricular synchronization. However, the benefit of triple-ventricular stimulation clearly needs confirmation in the most common group of patients for CRT, that is, sinus rhythm and ventricular conduction disturbance.

The results of the TRIP-HF study also raise pathophysiological questions: can addition of a third (anterior) lead improve synchrony of activation and contraction? Detailed electrical activation mapping studies have shown that the anterior wall is activated early during intrinsic rhythm in heart failure patients with LBBB (12), thus one would not select this as the single LV pacing site. Indeed, the number of nonresponders was shown to be higher using anterior than posterolateral LV lead placement (13). In addition, animal studies showed that no additional improvement can be expected when adding more LV pacing sites to a well-chosen one (14). The finding that adding anterior LV pacing to posterolateral wall stimulation seems to improve CRT is therefore not trivial and deserves further experimental and clinical investigation. One possible explanation for the beneficial effect observed during triple pacing is the technical approach used by the investigators, that is, the second LV lead was connected to the atrial port and was stimulated 25 ms before the RV and the first LV lead. Consequently, in the triple-site stimulation mode, CRT is not truly simultaneous but is sequential with moderate LV pre-excitation. It is known from both animal studies and patient research that on average, LV pre-excitation provides a better effect than simultaneous biventricular pacing. Thus, part of the benefit of the triple-site pacing in the TRIP-HF study might be explained by the sequential ventricular pacing.

Instead of adding more pacing sites, also attempting to position pacing leads to the LV endocardium may improve CRT. Even with larger numbers of epicardial pacing electrodes, the transmural gradient of activation is opposite of the physiological one. Endocardial LV pacing may avoid such a transmural activation abnormality. Endocardial LV pacing in heart failure is feasible using a trans-septal approach (15), and preliminary data show that it is superior to LV epicardial pacing (16). Upcoming technologies such as leadless pacing might enable a wider application of LV endocardial pacing.

In conclusion, the TRIP-HF study has delivered several important messages, but confirmation of the results in more common CRT populations and differentiating among patient categories, as well as comparison with other modalities for delivering multiple pacing sites, is mandatory. In addition, the technical challenges and the long-term safety issue related to the implantation of 2 transvenous LV leads should be remembered.

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