Can a New Algorithm of Cardiac Resynchronization Therapy (Adaptive CRT) Expand Its Utility?

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Cardiac resynchronization therapy (CRT) is an established essential strategy to manage patients with moderate to severe heart failure (HF).^{1–3} However, the obvious favorable effects of CRT in many randomized studies have been limited to patients with complete left bundle branch block (CLBBB) and a QRS width ≥ 150 ms.^{1–3}

Even in patients with severely wide QRS, several clinical studies have shown that CRT is least effective in those with complete right bundle branch block (CRBBB) and those with non-specific intraventricular conduction delay as compared with CLBBB patients.^{4,5} Furthermore, the EchoCRT study demonstrated that CRT is not effective, and even harmful, for reducing HF hospitalizations and deaths of patients with a narrow QRS < 130 ms and echocardiographic desynchronization.⁶ According to the results from the EchoCRT study, the ESC 2016 guidelines classified such patients as a Class III indication for CRT.⁷ On the other hand, a subanalysis of the EchoCRT study showed

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that CRT is not always harmful in the subgroup with a relatively small left ventricular volume.⁸ Based on this subanalysis, the lower limit of CRT indications in terms of QRS width was determined as 120 ms in the 2018 JCS/JHRS guidelines.⁹

Therefore, demonstrating CRT efficacy in patients with a moderately wide QRS or non-CLBBB QRS morphology is the next challenging frontier of this therapy, and much attention has been focused on whether the problem can be resolved by advanced capability of CRT or whether it is a fundamental limitation of CRT.

Under these circumstances, adaptive CRT (aCRT) has been introduced with great expectation that it will resolve some of the problems of CRT. The aCRT is a novel algorithm that periodically measures intrinsic atrioventricular (AV) conduction and dynamically adjusts CRT pacing

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conditions as necessary to maximize the effects of CRT. This algorithm also provides RV-synchronized LV pacing when AV conduction is normal and biventricular (BiV) pacing when AV conduction is prolonged (**Figure**).

This intriguing function has been evaluated by the Adaptive CRT study,¹⁰ a prospective, multicenter, randomized, double-blind clinical trial that compared CRT with the aCRT algorithm settings with conventional CRT with AV and VV settings optimized by a standardized echocardiographic protocol.

The main study and several subanalyses of the Adaptive CRT study found the following:

- aCRT was safe and at least as effective as conventional CRT with comprehensive echocardiographic optimization¹⁰
- RV pacing was reduced by 44% in the aCRT arm¹¹
- A higher percentage of synchronized LV pacing ($\geq 50\%$) was independently associated with decreased risk of death or HF hospitalization¹¹
- aCRT reduced the risk of AF compared with those receiving conventional CRT in the subgroups with prolonged AV conduction at baseline¹²
- aCRT was associated with improved patient outcomes over echo-optimized CRT in patients with preserved AV conduction, LBBB, and moderately wide QRS of 120–150 ms.¹³

The last point was reported by Yamasaki et al,¹³ using a clinical composite score including factors such as death, HF hospitalization, crossover from an assigned randomization, the NYHA class, and patient global assessment that categorizes patients as improved. Therefore, the clinical implication is rather indistinct.

A corresponding study by Ueda et al¹⁴ was designed to examine the clinical benefit of the aCRT algorithm in patients with mildly wide QRS (120–150 ms) or non-LBBB morphology. In this issue of the Journal, they demonstrate that aCRT significantly improved the composite clinical outcome of just 2 main endpoints (cardiac death and/or HF hospitalization). However, to promote use of aCRT with confidence in patients with a moderately wide QRS and/or non-CLBBB, several problems remain to be resolved. First, this study was retrospective with a small number of patients. Although the number of patients in each group was accidentally almost even, and much of the clinical background happened to be similar between the 2 groups, there might have been a concealed or unknown bias. Ideally, a prospective, large, randomized study, principally targeting patients with a moderately wide QRS and/or non-CLBBB is needed to obtain further strong evidence. Second, the authors do not explain why the primary endpoint decreased in the aCRT group despite the percentage of responders (defined as an improvement in the LVEF of $\geq 10\%$ and/or reduction in the LVESV of $\geq 15\%$) being comparable between the 2 groups (63% [aCRT group] vs. 59% [non-aCRT group], $P=0.42$). Third, the mechanism of the beneficial effect of the aCRT in these particular patients is still unclear. The authors speculate that the aCRT algorithm, which reduces unnecessary RV pacing, preserves a positive net effect of CRT and results in a better clinical outcome. However, their study did not show what percentage of RV pacing was avoided in the aCRT group. Further-

more, their speculation could not explain the beneficial effects of aCRT in patients with a wide and non-LBBB QRS.

Although the study by Ueda et al has several limitations, it shows us the expanding possibilities of CRT.

Disclosures

Takashi Kurita serves as a consultant to Japan Medtronic.

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