Cardiac Resynchronization Therapy
Antiarrhythmic or Proarrhythmic?*
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Cardiac resynchronization therapy (CRT) has become a well-established and important therapeutic option in the management of patients with symptomatic systolic heart failure. Improvement in quality of life and exercise tolerance as well as reduction in hospitalizations for heart failure have been demonstrated repeatedly (1,2). In addition, reverse ventricular remodeling and improvement in left ventricular ejection fraction are seen in the majority of patients. Reduction in mortality has also been shown, whether or not CRT is combined with an implantable cardioverter-defibrillator (ICD) (3). However, despite the fact that advanced heart failure is associated with an increased risk of sudden cardiac death, the effect of CRT on the risk of ventricular tachyarrhythmias has not been as clear cut.

Despite these favorable results, it is clear that epicardial left ventricular pacing reverses the normal direction of activation of the ventricle, leading to dispersion of repolarization and prolongation of the QT interval, which may be proarrhythmic (8,9). Case reports of patients who have had a marked increase in ventricular tachyarrhythmias after initiation of CRT support these observations from basic and animal studies (10).

Most studies of CRT have concentrated on patients with highly symptomatic heart failure. The success of this therapy has led to exploration of the role in CRT in less severe heart failure. In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) (11), patients with ischemic or nonischemic cardiomyopathy, an ejection fraction of ≤0.30, New York Heart Association functional class I or II symptoms, and a QRS duration >130 ms were randomized to cardiac resynchronization therapy defibrillator (CRT-D) therapy or an ICD. There were 1,820 patients randomized in a 3:2 ratio and followed for an average of 2.4 years. The primary endpoint, death or a nonfatal heart failure event, was significantly reduced in the patients who received CRT-D therapy. In addition, CRT was associated with a significant reduction in LVESV and improvement in ejection fraction.

A number of studies have been performed in an attempt to elucidate the effect of CRT on ventricular arrhythmias. In studies that showed a beneficial effect of CRT, the main comparison has usually been between patients who did and those who did not receive CRT (4,5). The InSync ICD Registry, on the other hand, analyzed the risk of recurrent ventricular tachyarrhythmias in responders (defined as ≥10% decrease in left ventricular end-systolic volume [LVESV]) versus nonresponders and found a significant decrease in ventricular tachyarrhythmias in the responders (32% vs. 43%, p = 0.024) (6). In a retrospective analysis of the InSync III Marquis Study, a ≥15% reduction in LVESV was associated with a significant reduction in premature ventricular contractions and treated ventricular tachyarrhythmias (7).

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In the present substudy of the MADIT-CRT study, the risk of ventricular tachyarrhythmias was assessed during follow-up (12). Of the 1,820 patients in the main study, 1,372 patients had paired echocardiograms at baseline and at 1 year. The lack of echocardiographic data in most of the remaining patients was due to the fact that the U.S. Food and Drug Administration originally requested that CRT be turned off during the 1-year echocardiogram. Patients were divided into high responders (≥25% reduction in LVESV at 1 year post-implantation) and low responders (<25% reduction). The relatively high cutoff for response compared with some other studies was due to the fact that the overall response rate in the MADIT-CRT study was quite good, and a lower cutoff would have included a much smaller pool of patients in the low-responder group.

The risk of first appropriate ICD therapy for ventricular tachyarrhythmias was significantly reduced in high responders to CRT-D (12%) compared with low responders (28%); risk was intermediate in patients who received ICD therapy alone (21%) (p = 0.001 for the overall difference). High responders to CRT-D had a significant 55% reduction in the risk of ventricular tachyarrhythmias compared with ICD-only patients. Consistent with these observations, assessment of the response to CRT-D as a continuous variable showed a reduction of approximately 20% in all types of ventricular arrhythmias for every 10% reduction in LVESV.

Compared with ICD-only patients, low responders had a 34% increased risk (p = 0.08) for ventricular tachyarrhythmias or death and a 40% (p = 0.07) increased risk of ventricular tachyarrhythmias. Although not significantly

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different, the trend suggests that there may be an increased risk of ventricular tachyarrhythmias in low responders. If so, then epicardial pacing without achievement of ventricular remodeling may actually be proarrhythmic, making it critical that resynchronization be accomplished successfully.

By design, the MADIT-CRT study did not include patients with more symptomatic heart failure, and so it is not certain whether the results of this study would pertain to such patients. We also have no information on actual lead position in these patients. Left ventricular leads should be placed in a lateral or posterolateral position to maximize the chances of achieving resynchronization. Suboptimal lead position could promote ventricular tachyarrhythmias by dispersion of repolarization as well as by failure to achieve reverse ventricular remodeling with continued or progressive heart failure.

Despite these minor limitations, this study is valuable in that it confirms and extends the results of previous studies to a population of patients with milder heart failure. Key factors to note are the relatively long follow-up period, large number of patients in the study, different patient population compared with those of previous studies, and analysis of response as a continuous measure in addition to a dichotomous approach. Importantly, lack of response to CRT-D was associated with a greater frequency of ventricular tachyarrhythmias than patients treated with ICD therapy alone.

We can conclude that CRT in mild heart failure, when it is successful in promoting reverse ventricular remodeling, reduces the risk of ventricular tachyarrhythmias compared with ICD therapy alone. On the other hand, biventricular pacing with epicardial left ventricular pacing without improvement in ventricular size and function appears to be proarrhythmic. It is thus incumbent upon us to select patients for CRT carefully who have the most likelihood of responding to resynchronization and to make every effort to place the lead optimally. Demonstrable structural response to CRT remains the best insurance that patients will have optimal outcomes in follow-up.

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**REFERENCES**


**Key Words:** cardiac resynchronization therapy ■ heart failure ■ implantable cardioverter-defibrillator ■ reverse remodeling ■ ventricular arrhythmia.