Cardiac resynchronization therapy (CRT) has clearly been established as a mainstay therapy for patients with congestive heart failure (CHF), New York Heart Association functional class II to IV heart failure symptoms, and dyssynchrony. However, despite refinement in implantation techniques, improved technology, and careful patient selection, nonresponder rates are still approximately 30% (1). The role of ventricular arrhythmias (VAs) are inherent to the discussion of nonresponse to CRT. This topic has remained controversial because published data have not been consistent on whether VAs are increased, unaffected, or decreased by CRT (2–5).

In this issue of JACC: Clinical Electrophysiology, Saini et al. (6) attempt to further elucidate this topic by performing a meta-analysis of the following: 13 studies that evaluated VAs in patients who received CRT-defibrillators (CRT-D) versus patients who received only implantable cardioverter defibrillators (ICDs); 13 studies that evaluated VAs in echocardiographic responders versus nonresponders to CRT; and 3 studies that evaluated VAs in nonresponders who had been upgraded to a CRT-D from an ICD-only device.

In the first analysis group, 4,631 subjects were included; they had baseline left ventricular ejection fractions (LVEFs) of 21% to 32%, a QRS duration of >120 ms among the CRT-D patients, and a mean follow-up of 6 to 41 months. VAs were reduced in the CRT-D group compared with the ICD-only group (odds ratio [OR]: 0.804; 95% confidence interval [CI]: 0.695 to 0.928; p = 0.003). In the second analysis group, 3,667 subjects were included; they had a mean LVEF of 19% to 27%, a QRS mean duration of >150 ms, a mean follow-up of 6 to 57 months, and were categorized as responders or nonresponders based on 1 of 3 echocardiographic criteria as detailed in the study. VAs were reduced in CRT echocardiographic responders versus nonresponders (OR: 0.510; 95% CI: 0.429 to 0.607; p < 0.05). In the 3 studies of the third analysis group, a total of 1,183 CRT patients were included, 411 of whom were considered nonresponders by echocardiographic parameters; they had mean LVEFs of 26% to 30%, and a QRS mean duration of >130 ms. The investigators found more VAs in CRT nonresponders compared with ICD-only subjects (OR: 1.497; 95% CI: 1.225 to 1.829; p < 0.05).

Despite the limitations inherent to a meta-analysis, this ambitious study has significant clinical importance. Because of their correct observation that individual studies that examined the impact of CRT on VAs (particularly in nonresponders) have been small, retrospective, and nonrandomized, the meta-analysis is appropriate and can contribute to our understanding of the relationship of VAs in CRT, especially in light of patients’ response to CRT. Studies to date have not completely proven any of the commonly held theories as to why CRT can increase or decrease VAs. Pro-arrhythmia is believed to arise from the fact that epicardial pacing leads to reversal in the normal direction of activation in the ventricle, and thus, a dispersion of repolarization with prolongation of the QT interval (7,8). In contrast, antiarrhythmic effects of CRT are believed to arise from a diminished risk of myocardial ischemia due to improved cardiac output with reduced wall stress and a more advantageous neurohumoral impact on diseased myocardium (9).

The first analysis group in this study certainly corresponds with the general early findings from previous studies—that patients with severe LV dysfunction and dyssynchrony who received CRT...
showed a reduction in VAs (10). This likely reflects the fact that in all-comers with significant mechanical and electrical disturbances, most (approximately 70% who are responders) will benefit with reduced VA through one of the aforementioned antiarrhythmic mechanisms. Furthermore, the second analysis group confirmed the trend in follow-up studies that attempted to discover subgroups of CRT patients in the hope of improving patient selection and better prediction of who will benefit from CRT. Thus far, it seems responders, as defined by 1 of the echocardiographic parameters (post-implantation EF ≥35%, increase in LVEF by ≥5%, or reduction of LV end-systolic volume index by ≥10%), showed the most reduction in VAs as opposed to the nonresponders.

We do have some trepidation in fully endorsing the third group analysis, because, as the investigators mention, it only includes 3 studies. In addition, the treatment groups were fairly different, with only 1 study performing a direct comparison of the post-upgrade VA to pre-upgrade VA within the same patients (11). The other 2 studies either compared patients in whom the LV lead was turned “off” versus those in whom it was turned “on” (2) or patients who underwent CRT versus those who only received ICDs (12). However, this does serve to highlight the need for more prospective randomized data in the nonresponder group of patients.

Overall, the findings of this meta-analysis solidify the importance of CRT as an important treatment strategy in heart failure patients. It is not surprising that the CRT-D analysis versus the ICD analysis showed a significantly lower incidence of VAs in the CRT group, in whom reverse remodeling likely occurred in most of the patients. The finding of fewer VAs in the CRT responder group further establishes the critical importance of CRT response. This is particularly true in light of the investigators’ assertion of increased VAs in nonresponders compared with ICD-only patients (i.e., post-CRT upgrade compared with pre-CRT upgrade in the nonresponder population). Although the data in the third group are clearly limited, the suggestion of higher incidence of VAs in CRT nonresponders is thought-provoking and should compel us to continue working toward improved response rates, careful patient selection, and perhaps studying CRT nonresponders prospectively, by randomizing them to continued CRT versus turning their LV pacing leads off.

In addition, if we can reduce the nonresponder rate through improved patient selection, new pacing technology (e.g., multipoint pacing), or new optimization algorithms (e.g., adaptive CRT), will we then be able to also further reduce the incidence of VAs? More studies will clearly be needed to answer these questions. In the meantime, however, we should focus on the positive effects of CRT that have been nicely demonstrated in this meta-analysis, and although CRT and pro-arrhythmias remain in the discussion, the role of VAs in CRT (or vice versa) still remains locked in the proverbial “black box” at this time.

**REFERENCES**


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**KEY WORDS** cardiac resynchronization, non-responders, ventricular arrhythmias