Does Cardiac Resynchronization Help Patients with Cardiac Sarcoidosis?

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Abstract

This editorial discusses the report titled "Cardiac Resynchronization Therapy Response in Cardiac Sarcoidosis" by Shabtaie et al.

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In this issue of the journal, Shabtaie et al present a retrospective cohort study of the effects of cardiac resynchronization (CRT) in cardiac sarcoidosis (CS) in 55 patients managed at the Mayo Clinic enterprise from 2000-2021. A third of the patients had myocardial tissue diagnosis of CS, while 38% had probable CS and 29% had presumed CS. In a majority of patients, indications for CRT included QRS greater than 120 milliseconds with low LV ejection fraction (LVEF) <50% in 80% of patients and high degree AV block with reduced LV ejection fraction in 14.5% of patients. Positive response to CRT, defined as >5% improvement in LVEF from baseline, was seen in 23 patients (41.8%) at 6-months follow-up and in 26 patients (47.3%) at the last follow-up (at 4.1 ± 3.7 years). However, in the overall group, there was no statistically significant improvement in ejection fraction or left ventricular end-diastolic diameter at 6 months post-implantation

or at the last follow-up. Discussing these results and several other smaller cohorts, and the relatively poor outcomes of CS patients receiving CRT, authors raise the possibility of limited benefit of CRT in CS patients. There are, however, several important caveats that should prompt caution in drawing a strong conclusion.

This group included a relatively high percentage or cardiac-only involvement and patients in the category of "presumed CS". 47% of patients had extracardiac involvement, while 53% apparently had isolated cardiac involvement – which is more than was the 12% patients with isolated cardiac involvement reported in the multicenter registry from the Cardiac Sarcoidosis Consortium [1]. While it is impossible to ascertain the true incidence, this raises the possibility that some non-CS patients were included. Other conditions that can result in a positive PET scan (arrhythmogenic cardiomyopathy, non-sarcoid myocarditis, recent ablation) cannot be rule out in the absence of tissue diagnosis. CRT indications included QRS greater than 120 milliseconds with low LV ejection fraction (LVEF) <50% in 80% of patients, and baseline LVEF was 34.8 ± 10.9%. Some of these CRT devices were therefore implanted in patients with only mildly decreased LVEF (>35%) and/or only mildly prolonged QRS (<130-150 ms), therefore limiting the potential observed benefit of CRT. The authors explored the impact of several baseline characteristics on the response to CRT, but did not compare baseline left bundle branch block (LBBB) versus right bundle branch block (RBBB). 9 patients with baseline RBBB (16%) were included in the cohort, though currently most practitioners would not recommend CRT for these patients and their inclusion (most likely non-responders) may dilute the apparent benefit. Detailed information on the extent of LGE on MRI or FDG uptake on PET in these patients is not available. This might have played a role in their response to CRT – as the authors mention in their discussion. In terms of treatment, only 29% of patients were on steroids at the time of implant – steroids being generally considered the mainstay of immunosuppression therapy in these patients. However, "at 6 months post-implant, there was increased utilization of immunosuppression with 70.9% receiving corticosteroids, 23.6% methotrexate and 34.5% mycophenolate." We do not know how many patients were on *any*immunosuppressive therapy at a given point in time, the specific relationship of immunosuppressive therapy and presence of inflammation on PET, the intensity or duration of immunosuppression or the program of surveillance of disease activity. The patients included were enrolled as early as 2000, and PET-guided immunosuppression and surveillance, albeit not proven in randomized clinical trials, may be used more commonly in recent years. In any case, immunosuppressive treatment has been neither standardized, nor uniform by center or time period, therefore adding potential confounding effects to the results. Medical therapy for cardiomyopathy, while not specifically studied in CS patients, might have been suboptimal in this cohort, as suggested by numbers listed in Table 1 of the study by Shabtaie et al. Only 49.1% of patients were on ACE inhibitor, 16.45% on angiotensin II receptor blocker and 78.2% on beta-blocker.

Authors discuss possible reasons for limited benefits of CRT in CS patients. They discuss the possibility that extensive scar may limit benefits of CRT, similar to observations in ischemic cardiomyopathy (ICM). The potential role of scar also highlights the need and potential benefit of earlier diagnosis. In fact, the timing of diagnosis likely has improved over time, including during the duration of recruitment for this cohort. Earlier diagnosis may result in different patient characteristics and perhaps less extensive myocardial scarring, on average, in a more recent cohort. It is also worth mentioning that areas of scar noted in CS are often not transmural, so the same caveats seen in ICM patients with large, dense, transmural LV scars may not necessarily apply. Furthermore, areas of increased FDG uptake on PET scans are dynamic and may respond to immunosuppression. Suboptimal CRT pacing percentage (for example due to premature ventricular beats or atrial fibrillation) can also limit its benefits and attempts to maximize it should be part of routine clinical care. In this cohort, CRT pacing percentage was 95% initially and 97% at 6 months follow-up.

Most importantly, there has been no study of patients with CS and indication for CRT comparing outcomes between those who receive CRT and those who do not. Given these limitations, it is difficult to interpret the data and impossible to derive practice-changing conclusions. We are currently using recommendations for CRT based on data obtained in other populations and extrapolated to patients with CS.

CS is different from ICM with fixed scar or from other NICM. CS is often an active disease that has the potential to progress due to persistent and progressive inflammatory activity. Cardiomyopathy, LV systolic

dysfunction and arrhythmia could progress or fail to improve due to multiple mechanisms, including disease inflammatory activity, dyssynchrony from LBBB or RV pacing or progressive remodeling in the presence of irreversible myocardial damage. Consistent with other published data, the patients in this study had a high incidence of adverse outcomes: 20.0% went on to cardiac transplantation, 1.8% received left ventricular assist devices, and there was a high burden of ventricular arrhythmias during the follow-up period: by last follow up, 20.0% of patients had sustained ventricular tachycardia, 18.2% of patients had ICD shocks, and 16.4% of patients underwent ventricular tachycardia ablation. The relatively poor prognosis of these patients underscores the importance of optimizing and maximizing their management, and, along with the multidimensional nature of CS, leads us towards using a multipronged approach with all the tools that we have at our disposal: immunosuppression with the goal of adequate control of inflammation in order to prevent disease progression; optimal medical therapy of cardiomyopathy and CHF (as extrapolated from other populations of patients with cardiomyopathy); CRT and optimization of CRT pacing percentage (also by extrapolation from other studied populations). Inadequately addressing any of these aspects can lead to poor outcomes that may confound the results and dilute the apparent benefits of CRT.

It is true that same criteria and approaches we use in other cardiomyopathy populations may not extrapolate identically to CS. We need randomized clinical trials to inform and guide immunosuppressive therapy, the possible role of PET-guided immunosuppression or other medical therapy, or to identify the best candidates for device therapy. In this sense, this study tries to address an important question. It is worth repeating here the authors' call for "formulating prospective multicenter studies designed to assess the ideal CS patient to benefit from CRT therapy", and to extend it to other interventions and therapies in patients with CS. In the absence of better CS-specific data, recommendations for CRT in CS should continue to be based on data and guidelines from other populations of patients with cardiomyopathy[2-5].

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