Effect of Cardiac Resynchronization Therapy on Left Ventricular Remodeling in Patients With Cardiac Sarcoidosis

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Cardiac resynchronization therapy (CRT) has been shown to be beneficial in patients with medically refractory heart failure. Although it has been found to be effective in a wide range of etiologies for nonischemic cardiomyopathy, its role in improving remodeling and survival of patients with cardiac sarcoidosis (CS) remains undefined. We performed a retrospective review of all patients at our institution with CS who underwent implantation of a CRT device from 2007 to 2017. The outcomes of this population were compared with the outcomes of a cohort of patients with nonischemic cardiomyopathy with an etiology other than sarcoidosis. Nineteen patients in our institution with CS underwent CRT implantation during the time period. This group was compared with 311 consecutive patients with other etiologies of nonischemic cardiomyopathy who underwent CRT implantation. CRT improved left ventricular ejection fraction (LVEF) from 28.8% to 35.9% ($p < 0.05$) in CS, whereas it improved LVEF from 25% to 36.6% ($p < 0.01$) in non-CS group (difference in means of 0.13). CRT significantly improved diastolic and systolic LV diameters, mitral regurgitation, and right ventricular systolic function in non-CS patients but failed to improve same parameters in CS patients. In conclusion, CRT significantly improved LVEF in patients with CS. There is no significant evidence that survival outcomes of CRT patients with CS are significantly worse than other etiologies of nonischemic cardiomyopathy. © 2018 Published by Elsevier Inc. (Am J Cardiol 2019;123:329−333)

Cardiac resynchronization therapy (CRT) has evolved to be an important consideration for patients with heart failure and conduction abnormalities. The CARE-HF, COMPANION, MADIT-CRT, and RAFT trials together demonstrated a significant benefit in mortality and left ventricular (LV) recovery in patients with heart failure with an ejection fraction $<35\%$ and widened QRS ≥ 120 ms.[1−4] Sarcoidosis is an autoimmune condition that leads to the deposition of granulomas[5] and infiltrates the heart in approximately 25% of cases, where it can lead to wide spectrum of cardiac maladies.[6] Because treatment of systemic sarcoidosis is targeted with immunosuppression, the optimal treatment of cardiac sarcoidosis (CS) remains unknown. *The Heart Rhythm Society Expert Consensus Statement on the Management of Arrhythmias Associated with Cardiac Sarcoidosis* published in 2014 states that the indications for pacing should be the same as other patients who have atrioventricular (AV) block or chronic bifascicular block.[7] Furthermore, the committee recommended implantable cardioverter defibrillators as a class 1 recommendation in patients with cardiogenic sarcoidosis with spontaneous sustained ventricular arrhythmias and previous cardiac arrest, or LV ejection fraction (LVEF) $\leq 35\%$ despite optimal medical therapy and a period of immunosuppression.[7] However they state that "there are no specific data related to the use of cardiac resynchronization therapy in CS patients and in general device guidelines should apply to CS patients."[7] Given the limited information available concerning CRT in the CS population, we sought to report our single-center experience with CRT in the CS population.

Methods

We retrospectively reviewed all CRT patients from 2007 to 2017 with a diagnosis of CS. The Cleveland Clinic Institutional Review Board approved this study. We identified 19 patients during this time period who had a confirmed diagnosis of CS. For establishment of the diagnosis of CS, 3 patients were diagnosed using histological criteria through endomyocardial biopsy and 16 were diagnosed invoking the clinical diagnostic group criteria as outlined in the Heart Rhythm Society 2014

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guidelines,[7] including typical advanced imaging modality abnormalities (PET and magnetic resonance imaging), and unexplained cardiomyopathy, in the presence of histologically proved diagnosis of extracardiac sarcoid. Our CS cohort was compared with 311 consecutive patients with nonischemic cardiomyopathy with an etiology other than CS, who underwent CRT implantation during the same period. The data from this group were used more as a reference to compare CS patients undergoing CRT rather than true comparator.

Detailed baseline demographic and clinical characteristics were obtained on all 19 CS patients and 311 non-CS patients. All patients had medication refractory heart failure and received extensive cardiac workup including electrocardiography, echocardiography, laboratory testing, stress testing, cardiac catheterization, and advanced cardiac imaging with cardiac magnetic resonance imaging and or PET-FDG as indicated. The end points that were assessed were changes in LVEF, LV end-diastolic and systolic diameters, degree of severity of mitral regurgitation, and right ventricular (RV) systolic function with echoes performed closest to 6 months after implantation but no earlier than at least 2 months after implantation of CRT.

LVEF was measured and defined via a combination of volumetric analysis using Simpson's biplane and visual estimation and was retrospectively obtained via chart review. Mitral regurgitation was defined on a scale from 0 to 9 and RV systolic function was measured on a scale from 0 to 5. Response to CRT was defined as an improvement in LV systolic function $\geq 5\%$ at the time of follow-up echo at least 2 months and closest to 6 months after implant. Mortality was assessed using the electronic medical record, US Social Security Death Index, and online obituary search. In addition to deaths, our end point for our Kaplan-Meier was defined as heart failure progression including deaths, LV assist device implantation, and cardiac transplantation.

All continuous variables are presented as mean $\pm$ standard deviation. All categorical variables are presented as absolute numbers and percentages. Comparisons were made using Fisher's exact test for discrete variables and Students' *t* test for continuous variables. Factors known to be possibly associated with CRT response (age, gender, QRS duration, left bundle branch block, beta-blockers, ace inhibitor were entered into a multivariable model to determine their significance in prediction of CRT response in our cohort. Presence of CS was then added to the model to determine whether any differences in outcomes existed. Survival function between CS and non-CS was compared using a Kaplan-Meier survival analysis with a log-ranked test.

For all analyses, a 2-tailed $p < 0.05$ was considered statistically significant. All analyses were performed using GraphPad Prism (GraphPad Software, Inc., La Jolla, California) and/or SAS (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics of the study population are displayed in Table 1. Pre- and postimplantation echocardiograms were available for 18 of the 19 patients in the CS group and 221 of the 311 patients in the non-CS group. Of the 18 CS patients with follow-up echoes, 14 were on corticosteroids at the time of implantation of CRT. Seven patients were on methotrexate in addition to corticosteroids, whereas 1 was solely on methotrexate. No other immunosuppressants were used at the time of implant. Even with ongoing immunosuppression, 0 of the 19 CS patients had device infection at follow-up.

Table 1
Baseline characteristics

Variable	Sarcoidosis		p value
	Yes (n = 19)	No (n = 311)	
Age (years)	54.5 ± 9.3	63.7 ± 13.7	0.0005*
Males	12 (63%)	160 (51%)	0.35
Defibrillator	18 (95%)	278 (89%)	0.71
Left-bundle branch block	11 (58%)	205 (66%)	0.47
QRS duration (ms)	143 ± 28	151 ± 26	0.27
High grade atrio-ventricular block	5 (26%)	22 (7%)	0.01*
Atrial fibrillation	5 (26%)	142 (46%)	0.15
Smoker	7 (37%)	159 (51%)	0.25
Hypertension	10 (53%)	173 (56%)	0.82
Hyperlipidemia	6 (32%)	141 (45%)	0.34
Chronic obstructive pulmonary disease	0	38 (12%)	0.14
Diabetes mellitus	1 (5%)	83 (27%)	0.053
Cerebrovascular accident	0	16 (5%)	0.61
Brian natriuretic peptide (pg/mL)	332 ± 286	573 ± 775	0.08
Creatinine (mg/dL)	1.1 + 0.4	1.1 ± 0.6	0.69
Beta-blocker	15 (79%)	277 (89%)	0.25
Angiotensin-converting enzyme inhibitor	16 (84%)	249 (80%)	1.00
Diuretic	9 (47%)	221 (71%)	0.04*
Digoxin	1 (5%)	60 (19%)	0.22
Anti-arrhythmics	1 (5%)	32 (10%)	0.71

* Defined as $p < 0.05$.

As displayed in Figure 1, CS patients saw a significant improvement in LVEF from a mean of 28.8 to 35.9 ($p < 0.05$), which is similar to non-CS improvement in LVEF from 25 to 36.6 ($p < 0.01$) at a mean combined follow-up of 15.3 $\pm$ 17.0 months. CS patients failed to achieve a significant improvement in other parameters of reverse remodeling.

Of the CS patients, 11 of the 18 patients (61.1%) showed an improvement of at least 5% on follow-up echoes. This was comparable to the non-CS cohort of which, 157 of the 221 patients (71.0%; $p = 0.42$) had an improvement of at least 5% on follow-up echoes performed. In a multivariable model without including sarcoidosis, age, gender, QRS duration, beta-blocker use, and ACEi use were not significantly associated with CRT response. Left bundle branch block was significantly associated with response to CRT with an odds ratio of 2.98 (95% confidence interval: 1.43 to 6.22). The addition of CS to the model had no significant change in the model as presence of CS had an odds ratio of 0.721 (95% confidence interval: 0.260 to 2.003). In the revised model with CS as a variable, variables other than left bundle branch block had no effect on CRT response. Of

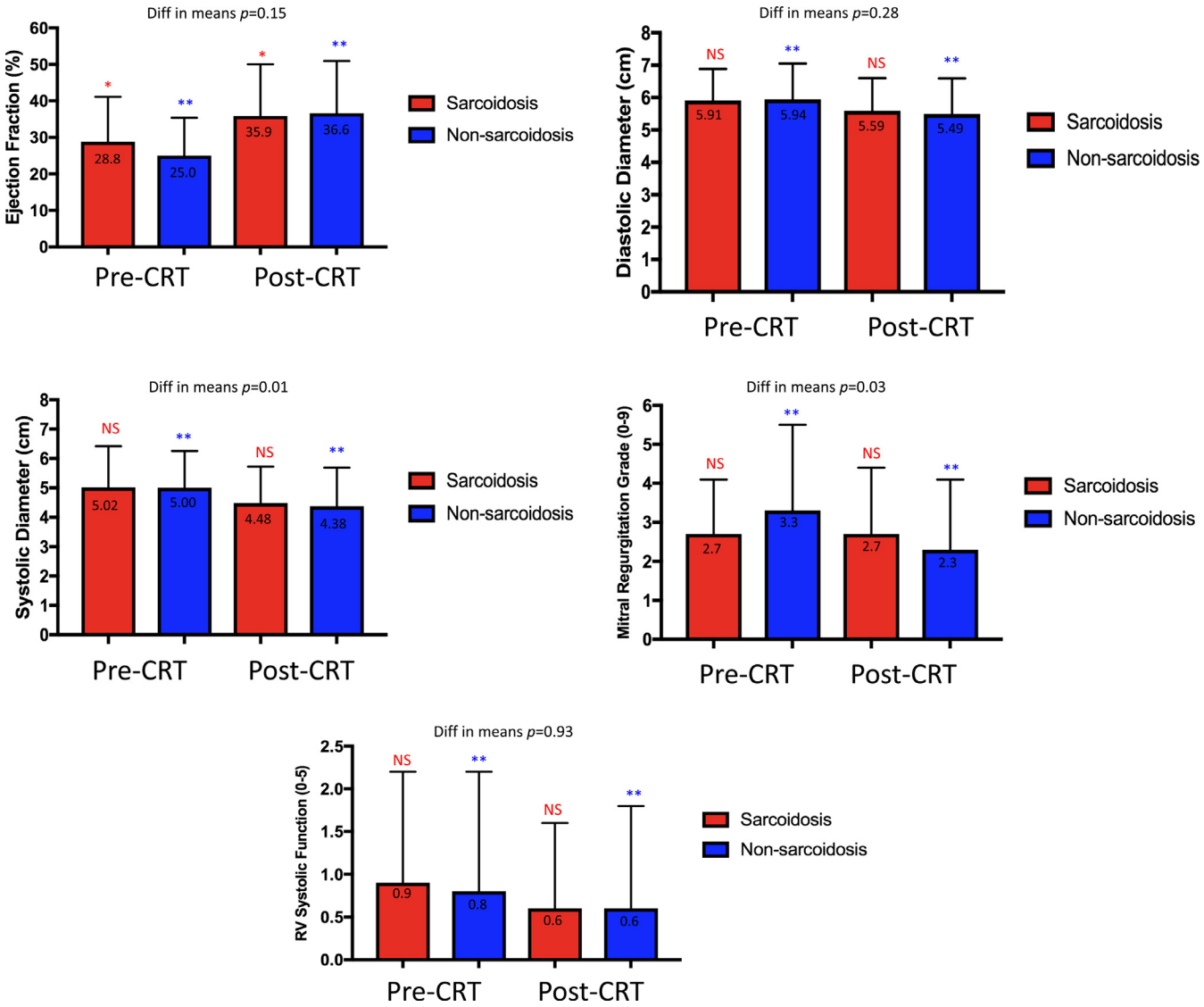

Figure 1. Bar graphs representing change in LV ejection fraction, diastolic/systolic diameters, mitral regurgitation, right ventricular systolic function after CRT in CS, and noncardiac sarcoidosis patients. Bar graph with number represents mean with error bar representing standard deviation. NS = nonsignificant; ** = p $<$0.01. Difference in means calculated with Student's *t* test between pre- and post-means between both groups.

the 14 CS patients with New York Heart Association before and after data, patients significantly improved from a mean New York Heart Association class of 2.4 $\pm$ 0.6 to 1.8 $\pm$ 0.6 (p = 0.021) at a mean follow-up of 7.6 $\pm$ 3.3 months.

Of the 19 patients with CS, 5 (26.3%) died, required implantation of an LVAD, or required cardiac transplantation, whereas of the 311 patients with non-CS, 108 (34.7%; p = 0.62) met their survival end point at a combined mean follow-up of 75.6 $\pm$ 35.1 months. As seen in Figure 2, a Kaplan-Meier survival function curve showed no significant difference in mortality in the 2 groups after implantation of a CRT device (p = 0.90).

Discussion

The main findings of this study are that CRT significantly improved LVEF in patients with CS, similar to levels seen in other etiologies of nonischemic cardiomyopathy who also received CRT. Survival after CRT implantation in patients with CS is no worse than patients with non-CS.

The published data on the role of CRT in patients with CS is limited. To our knowledge, our study is the first study to examine the effects of CRT in a population of CS patients in the United States. Two studies about outcomes for CRT patients with CS exist and are published by groups in Japan describing results in a Japanese population. Yufu et al compared CS patients with CRT with dilated cardiomyopathy patients and found a higher rate of major adverse cerebral and cardiovascular events in patients with CS.[8] Response to CRT was lower in the CS cohort compared with patients with dilated cardiomyopathy.[8] Sairaku et al reported their experience with 18 CS patients implanted with CRT and found no difference between baseline LVEF and LV systolic volume at baseline and 6-month follow-up.[9]

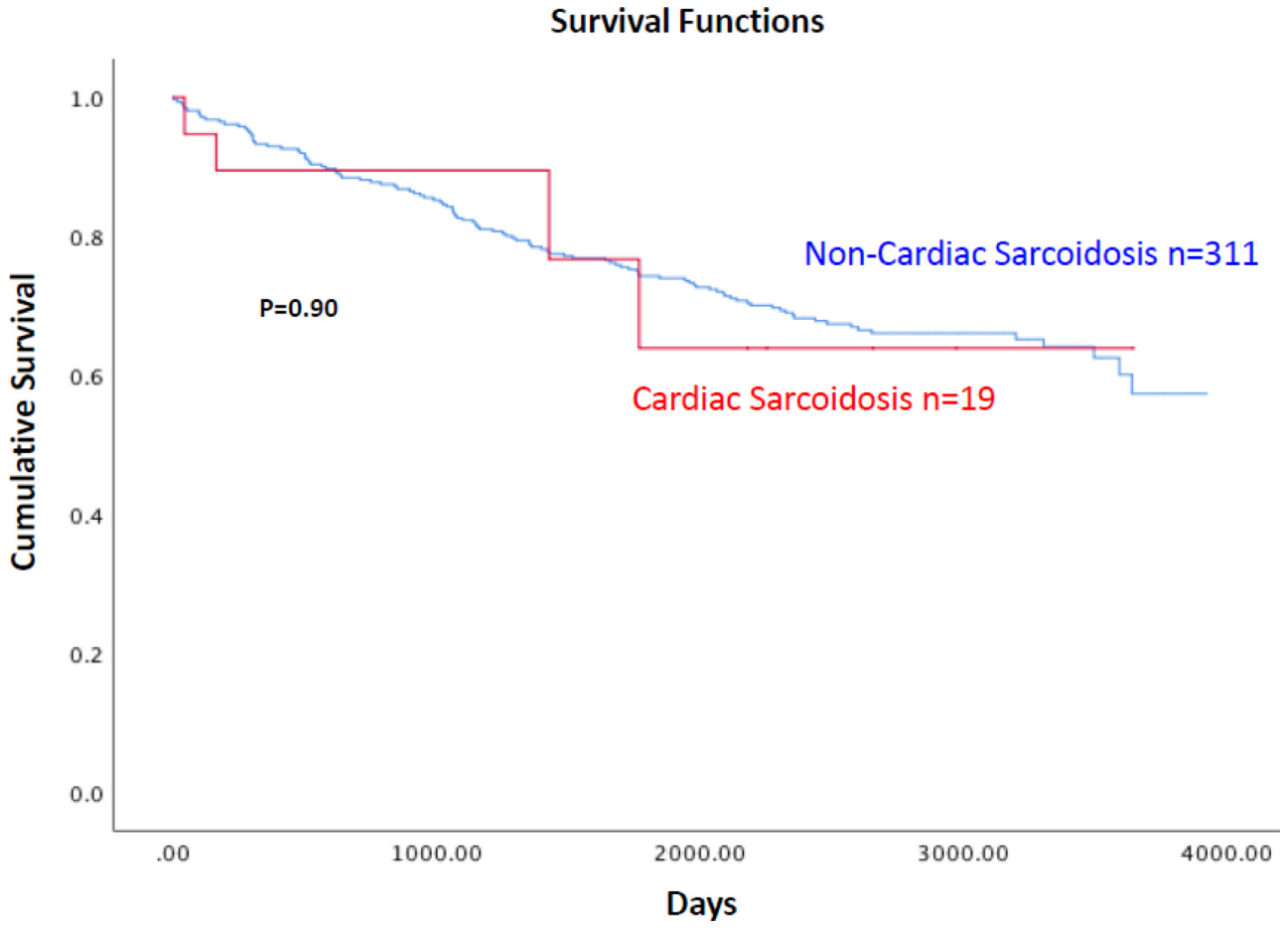

Figure 2. Kaplan-Meier curve demonstrating survival comparison between patients with sarcoidosis and patients with noncardiac sarcoidosis. Survival was measured as days after CRT to death, LVAD, or transplant.

The explanation for the low responder rate in the former study by Yufu et al compared with our study likely relates to their definition of CRT response (ours was defined as improvement of ejection fraction of at least 5%, whereas Yufu et al[8] used 15% end systolic volume calculation). As seen in this study, and others[10] the use of multiple parameters to define CRT response is optimal and CS as a cardiomyopathy etiology is not different. Although Sairaku et al measured ejection fraction as a marker for CRT response and found no difference 6 months after implant, the difference between our results and theirs may be because a majority of their patients received CRT upgrades as opposed to de novo CRT devices.[9] Furthermore, our study had a higher proportion of patients with left bundle branch block compared with Saiarku et al (58% vs 28%).[9] Importantly, because the previously mentioned 2 studies add to existing knowledge on CS, we acknowledge the heterogeneity and dynamic nature of inflammation and scar that define cardiomyopathy related to CS and there may be a difference in the make-up of CS patients depending on geographic and racial backgrounds. Previous studies have found a higher rate of involvement and death in Japanese patients with CS than African-Americans and Caucasians with CS, which could explain why the CS seen in Japanese populations may not be the same seen in the United States and which could account for our higher rate of left bundle branch block, better CRT response, and outcomes in patients with CRT.[11] Our study also suggests that the mechanism of CRT improvement in patients with CS may be different from patients with non-CS. CS patients with CRT may see improvements secondary to ongoing immunosuppressive use or due to correction from obligate RV pacing from high degree AV block.

Given our study's findings, it is reasonable to follow current guidelines and consider implantation of a CRT device in patients with CS who meet traditional criteria based on LVEF, QRS duration and morphology, and symptom burden. CRT also should be implanted in patients with reduced EF and high degree AV block. Our study supports an improvement in LVEF after CRT implantation and no difference in mortality between patients with CS and non-CS. There were also no device related infections in the CS group, which is especially important given the ongoing immunosuppression.

Our study has several limitations that should be acknowledged. First, this is a retrospective study done at a single institution. Second, mortality data were assessed as all-cause mortality and individual causes were not

ascertained. Lastly, our follow-up echoes were not done at specific time points but at the discretion of individual patient's cardiologists.

In conclusion, patients with CS showed an improvement in LVEF after CRT implantation which is similar to the improvement seen in patients with other etiologies of nonischemic cardiomyopathy. There was no significant difference in mortality between patients with CS versus those with other causes of nonischemic cardiomyopathy after implantation of a CRT device.

1. Cleland JGF, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Cardiac Resynchronization-Heart Failure (CARE-HF) study investigators. The effect of cardiac resynchronization therapy on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–1549.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) investigators. *N Engl J Med* 2004;350:2140–2150.
3. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D. Zareba W MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329–1338.
4. Tang AS, Wells GA, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Resynchronization-defibrillation for ambulatory heart failure trial investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;363:2385–2395.
5. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. *Lancet* 2014;383:1155–1167.
6. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid. A clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation* 1978;58:1204–1211.
7. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, Judson MA, Kron J, Mehta D, Cosedis Nielsen J, Patel AR, Ohe T, Raatikainen P, Soejima K. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* 2014;11:1305–1323.
8. Yufu K, Kondo H, Shinohara T, Kawano K, Ishii Y, Miyoshi M, Imamura T, Saito S, Okada N, Akioka H, Teshima Y, Nakagawa M, Takahasi N. Outcome of patients with cardiac sarcoidosis who received cardiac resynchronization therapy: comparison with dilated cardiomyopathy patients. *J Cardiovasc Electrophysiol* 2017;28:177–181.
9. Sairaku A, Yoshida Y, Nakano Y, Hirayama H, Maeda M, Hashimoto H, Kihara Y. Cardiac resynchronization therapy for patients with cardiac sarcoidosis. *Europace* 2017;19:824–830.
10. Rickard J, Baranowski B, Wilson Tang WH, Grimm RA, Niebauer M, Cantillon D, Wilkoff BL, Varma N. Echocardiographic Predictors of Long-Term Survival in Patients Undergoing Cardiac Resynchronization Therapy: What Is the Optimal Metric? *J Cardiovasc Electrophysiol* 2017;28:410–415.
11. Iwai K, Sekiguti M, Hosoda Y, DeRemee RA, Tazelaar HD, Sharma OP, Maheshwari A, Noguchi TI. Racial difference in cardiac sarcoidosis incidence observed at autopsy. *Sarcoidosis* 1994;11:26–31.