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Early and frequent defibrillator discharge in patients with cardiac sarcoidosis compared with patients with idiopathic dilated cardiomyopathy

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ABSTRACT

Background: Little is known about the suitability of implantable cardioverter defibrillator (ICD) implantation in patients with cardiac sarcoidosis (CS). We evaluated the efficacy of ICD implantation in patients with CS, including suspected CS, compared with those with idiopathic dilated cardiomyopathy (DCM).
Methods: A total of 102 consecutive patients with definite CS, suspected CS, or DCM who underwent ICD implantation were enrolled. The endpoint was the first documentation of appropriate ICD therapy for ventricular tachyarrhythmias. The follow-up started after ICD implantation.
Results: Appropriate ICD therapies occurred in 15 (56%) of 27 patients with definite CS, 17 (68%) of 25 with suspected CS, and 16 (32%) of 50 with DCM. The rate of appropriate ICD therapies was higher in patients with definite CS and those with suspected CS than in those with DCM (log-rank test, $p = 0.010$). After ICD implantation, five or more appropriate ICD therapies occurred in 5 (19%) patients with definite CS and 10 (40%) with suspected CS, but in only 1 (2%) with DCM. Cox proportional hazard analysis showed that CS, including suspected CS, was independently associated with appropriate ICD therapies. For primary prevention, the rate of appropriate ICD therapies was higher in patients with CS than in those with DCM (log-rank test, $p = 0.034$). More than half of patients with CS received appropriate ICD therapies.
Conclusions: Patients with CS receive appropriate ICD therapies for ventricular tachyarrhythmias at a higher rate, compared with those with DCM, suggesting that ICD implantation should be performed in patients with CS.

1. Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology [1]. Cardiac involvement [cardiac sarcoidosis (CS)] is associated with an increased risk of mortality [2]. Patients with CS have a worse prognosis than those with idiopathic dilated cardiomyopathy (DCM) [3]. However, little is known about the risk of sudden death in patients with CS, compared with those with DCM. Large prospective trials in patients with DCM have shown a protective effect of implantable cardioverter defibrillator (ICD) implantation on sudden death [4–6], and the indication for ICD implantation is based on the severity of left ventricular (LV) dysfunction. On the other hand, CS is listed as a class IIa indication for ICD implantation irrespective of LV function [7], but the data regarding the suitability are limited. In addition, definitive diagnosis of CS is difficult. Some patients are recognized as suspected CS in the clinical setting, that satisfies the guideline-established clinical cardiac findings, but do not meet the criteria for definite CS because of the absence of histological confirmation or extracardiac sarcoidosis [8,9]. As in patients with definite CS, ICD implantation may also be effective in patients with suspected CS. Therefore, we evaluated the efficacy of ICD implantation in patients with CS, including suspected CS, compared with those with DCM.

2. Methods

2.1. Study population

We enrolled 102 consecutive patients who were diagnosed with definite CS, suspected CS, or DCM and underwent ICD implantation from January 2006 to March 2015. The diagnostic guidelines for CS [8,9] are shown in Supplementary Table 1. In brief, CS is diagnosed on the basis of histological or clinical confirmation. Histological diagnosis is confirmed when endomyocardial biopsy demonstrates non-caseating epithelioid cell granulomas. In the absence of histological confirmation, clinical diagnosis is confirmed when extracardiac sarcoidosis is diagnosed and the clinical cardiac findings (more than two of four major findings, or one of four major findings and more than two of five minor findings) are satisfied. Major findings comprise advanced atrioventricular block,

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basal thinning of the interventricular septum, positive myocardial uptake of gallium-67 citrate (^{67}Ga) scintigraphy, and LV ejection fraction (EF) <50%. Minor findings comprise abnormal electrocardiogram, abnormal echocardiography, perfusion defect on myocardial scintigraphy, delayed myocardial enhancement on magnetic resonance imaging, and fibrosis or monocyte infiltration on endomyocardial biopsy.

Definite CS was defined as the presence of histologically or clinically confirmed CS according to the guidelines [8,9]. Suspected CS was defined as a suspicion of CS in the clinical setting and the presence of guideline-established clinical cardiac findings (more than two of four major findings, or one of four major findings and more than two of five minor findings), but the absence of definite CS because of the lack of histological confirmation or extracardiac sarcoidosis [10]. DCM was defined as the presence of LV dysfunction in the absence of any other known causes of myocardial abnormalities. All patients underwent endomyocardial biopsy and clinical examinations to rule out other myocardial diseases, including giant cell myocarditis, arrhythmogenic right ventricular cardiomyopathy, connective tissue disease, and ischemic heart disease.

All patients gave written informed consent. This study was performed according to the principles of the Declaration of Helsinki and was approved by our institutional ethics committee.

2.2. ICD implantation and follow-up

The indication for ICD implantation was at the discretion of the treating physicians. ICD programming was at the discretion of the implanting and treating physicians. Patients were followed at the device clinic every 3–6 months. The device was interrogated at the scheduled and event-driven visits, and ICD therapies were reviewed by experienced cardiologists in our institution. To distinguish ventricular tachyarrhythmias, intracardiac recordings were analyzed with respect to rate, onset, regularity, stability, and morphology. Clinically relevant ventricular tachyarrhythmias were selected. An appropriate ICD therapy was defined as anti-tachycardia pacing (ATP) or a shock delivered during ventricular tachyarrhythmias. Electrical storm was defined as three or more appropriate ICD therapies for ventricular tachyarrhythmias within 24 h. An inappropriate ICD therapy was ATP or a shock resulting from supraventricular tachyarrhythmias, T wave oversensing, or lead noise. The endpoint of this study was the first documentation of appropriate ICD therapy (ATP or shock) for ventricular tachyarrhythmias. The follow-up started at the time of ICD implantation and continued until October 2016.

2.3. Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and as number and percentage for categorical variables. Continuous variables were compared among the three groups by one-way analysis of variance for normally distributed variables and by the Kruskal-Wallis test for non-normally distributed variables, and were compared between the two groups by the *t*-test and the Mann-Whitney *U* test. Categorical variables were compared by the chi-square test. The cumulative rate of appropriate ICD therapies was estimated using Kaplan-Meier analysis, and the difference was analyzed using the log-rank test. Predictors of appropriate ICD therapies were analyzed using Cox proportional hazard analysis. Variables for the univariate analysis included age, sex, New York Heart Association functional class, LVEF, the presence of non-sustained ventricular tachyarrhythmia defined as ≥6 consecutive ventricular premature beats at a rate ≥120 bpm lasting <30 s, the presence of permanent atrial fibrillation, QRS duration, QTc interval, amiodarone use, and CS. Variables with a p value <0.10 in the univariate analysis were entered into the multivariate analysis. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). Statistical analysis was performed with JMP version 8.0 (SAS Institute Inc., Cary, NC), and a p value of <0.05 was considered statistically significant.

3. Results

3.1. Definite and suspected CS

Definite CS was diagnosed in 27 patients, including 13 with histological confirmation by endomyocardial biopsy and 14 with clinical confirmation. Among them, lung involvement was observed in 19 patients, skin involvement in 5 patients, and eye involvement in 5 patients. Suspected CS was diagnosed in 25 patients. Regarding the CS diagnostic guidelines' clinical cardiac findings, 21 patients satisfied more than two of four major findings and 4 patients satisfied one of four major findings and more than two of five minor findings. The clinical cardiac findings in patients with definite CS and those with suspected CS are shown in Supplementary Table 2. Except for positive myocardial uptake of ^{67}Ga scintigraphy, the clinical cardiac findings were similar between the two groups.

3.2. Clinical characteristics in the study population

The study population comprised 27 patients with definite CS, 25 with suspected CS, and 50 with DCM. The mean age of the patients was 62 ± 14 years. Sixty-two (61%) patients underwent ICD implantation for primary prevention of sudden death, and 40 (39%) patients underwent for secondary prevention. The median period from the diagnosis of definite CS, suspected CS, and DCM to ICD implantation was 1 month (range, 0–109 months). The mean LVEF was 33 ± 12%. Ninety-five (93%) patients were treated with beta-blockers, and 32 (31%) patients were treated with amiodarone.

Clinical characteristics among patients with definite CS, suspected CS, and DCM are shown in Table 1. LVEF was lower in patients with DCM than in those with definite CS and those with suspected CS. Advanced atrioventricular block was frequently observed in patients with definite CS and those with suspected CS. Twenty (74%) patients with definite CS and 3 (12%) with suspected CS were treated with steroids, that prednisone was initiated at a dose of 30 or 40 mg daily and tapered over a period of 6–12 months to maintenance a dose of 5–10 mg daily. The other 7 patients with definite CS were not treated with steroids because of the decision of the treating physicians or patient refusal. The 22 patients with suspected CS were not treated with steroids because of the lack of definitive diagnosis of CS, whereas the 3 patients were treated based on the decision of the treating physicians because they satisfied all four major findings of the diagnostic guidelines for CS and were considered to have a high possibility of CS. No patients started steroid treatment during the follow-up period. There were no significant differences in age, New York Heart Association functional class, frequency of non-sustained ventricular tachyarrhythmia, or medications such as beta-blockers and amiodarone among the three groups.

3.3. ICD therapy

During a median follow-up of 24 months (range, 1–113 months), appropriate ICD therapies occurred in 15 (56%) of 27 patients with definite CS, 17 (68%) of 25 patients with suspected CS, and 16 (32%) of 50 patients with DCM. The causative arrhythmia of the appropriate ICD therapies was ventricular fibrillation in 2 patients and sustained ventricular tachyarrhythmia in 46 patients. Ventricular fibrillation occurred in 1 (4%) patient with definite CS and 1 (4%) with suspected CS. Polymorphic ventricular tachyarrhythmias occurred in 2 (7%) patients with definite CS, 1 (4%) with suspected CS, and 1 (2%) with DCM. Monomorphic ventricular tachyarrhythmias occurred in 11 (41%) patients with definite CS, 16 (64%) with suspected CS, and 15 (30%) with DCM. The mean heart rate of ventricular tachyarrhythmias was 184 ± 25 bpm in patients with definite CS, 192 ± 28 bpm in those with suspected CS, and 179 ± 18 bpm in those with DCM. Syncope due to ventricular tachyarrhythmias occurred in 4 (15%) patients with definite CS, 4 (16%) with suspected CS, and 1 (2%) with DCM. The incidence of syncope was higher in patients with definite CS and those with suspected CS than in those with DCM ($p = 0.040$). The appropriate ICD therapy was ATP in 32 patients and a shock in 16 patients. The shock occurred in 5 (19%) patients with definite CS, 7 (28%) with suspected CS, and 4 (8%) with DCM. Kaplan-Meier analysis showed that the rate of appropriate ICD therapies was higher in patients with definite CS and those with suspected CS than in those with DCM (log-rank test, $p = 0.010$) (Fig. 1). The rate of appropriate ICD therapies was not different between patients with definite CS and those with suspected CS (log-rank test, $p = 0.486$).

The frequencies of appropriate ICD therapies after ICD implantation are shown in Supplementary Fig. 1. During a median follow-up of 46 months, five or more appropriate ICD therapies occurred in 5 (19%) patients with definite CS and 10 (40%) patients with suspected CS, but in only 1 (2%) patient with DCM. Electric storm was observed in 4 (15%) patients with definite CS, 7 (28%) patients with suspected CS, and 1 (2%) patient with DCM.

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