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Effect of Cardiac Rehabilitation in Preventing Implantable Cardioverter Defibrillator Therapy in Patients with Reduced Left Ventricular Ejection Fraction

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Abstract: In patients with implantable cardioverter defibrillators (ICD) or cardiac resynchronization therapy defibrillators (CRT-D), appropriate and inappropriate shocks lead to a higher risk of mortality. Cardiac rehabilitation (CR) is an established therapy for patients with ischemic heart disease and/or congestive heart failure. However, it is unclear whether CR could reduce the need for device therapies. The purpose of the present study was to investigate whether CR reduces device therapies and mortality in patients with severe cardiac dysfunction and ICD or CRT-D. Of the 390 patients who were implanted with an ICD or CRT-D between 1998 and 2015, 222 (178 men, 44 women) with a low ejection fraction (EF; < 45%) were investigated in this present study. The study cohort was divided into two groups, the CR group (n = 70) and the non-CR group (n = 152), and baseline clinical characteristics of the two groups were compared. Furthermore, the number of all device therapies, appropriate therapies, inappropriate therapies, and mortality for 1 year after ICD or CRT-D implantation were compared. There were no significant differences in baseline characteristics between the CR and non-CR groups (e.g. age 68.5 vs 66.2 years [$P = 0.16$]; EF 27.9% vs 29.7% [$P = 0.14$]). Kaplan-Meier analysis revealed that all device therapy events and inappropriate therapy events were lower in the CR than non-CR group ($P = 0.01$ and $P = 0.03$, respectively). Appropriate therapy events and mortality did not differ significantly between the two groups (5.7% vs 13.1% [$P = 0.09$] and 11.4% vs 17.0% [$P = 0.28$], respectively). CR may have beneficial effects in preventing therapy events, especially inappropriate therapy, in patients with an ICD or CRT-D.

Key words: cardiac rehabilitation, ICD, therapy event, inappropriate therapy event

Introduction

Implantable cardioverter defibrillators (ICDs) have been shown to be efficacious against

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sudden cardiac death (SCD) in patients with ventricular fibrillation (VF) or ventricular tachycardia (VT)[1-4]. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) demonstrated the efficacy of ICD therapy in patients with ischemic heart failure[5], whereas the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed that patients with a low left ventricular ejection fraction (LVEF) benefitted from ICD therapy[6]. Recently, the indications for ICD implantation have expanded. Conversely, one study has demonstrated that appropriate or inappropriate shocks are one of the risk factors for prognosis[7], and subanalysis of data from MADIT-II and SCD-HeFT showed a two-fold increased risk of death in patients who experienced inappropriate ICD shocks[8, 9]. New strategies, changing the detection time and zone for ventricular arrhythmia, have been proposed to reduce inappropriate shocks[10-13]. However, these new strategies cannot completely prevent ICD shocks and we must to try avoid any shocks. Cardiac rehabilitation (CR) is an established therapy for patients with ischemic heart disease and/or congestive heart failure that has been shown to have various benefits, such as increasing exercise ability, psychological functioning, and improving prognosis[14-18]. However, it is unclear whether CR can reduce the use of device therapies in patients with an ICD or cardiac resynchronization therapy defibrillator (CRT-D). Therefore, the aim of the present study was to investigate the effects of CR in patients with an ICD or CRT-D who had a low ejection fraction (EF).

Methods

Patients and study protocol

The present study was a retrospective analysis. Of the 390 patients implanted with an ICD or CRT-D between 1998 and 2015 institutional ethics committee at our institution, 222 (57%) were found to have a low LVEF (< 45%) before implantation, as determined by echocardiography. These 222 patients were divided into two groups, the CR group (n = 70) and the non-CR group (n = 152). The CR group consisted of patients who started CR immediately before or after ICD or CRT-D implantation, whereas the non-CR group consisted of patients who did not undergo CR during the follow-up period. If patients were upgraded from pacemakers to ICDs or CRT-Ds, the day on which the upgrade occurred was considered the start date for the follow-up period. The follow-up period was 1 year after implantation of the device. The primary endpoint was device therapy. Patients were excluded from the study if: (i) CR was not started immediately before and/or after device implantation; (ii) they did not make any hospital visits after discharge; and (iii) they had a history of cardiac surgery within 1 month after implantation.

The present study was approved by the institutional ethics committee at our institution.

Measurements

ICD therapies after implantation were evaluated using device reports. In addition, the application of shock therapy and anti-tachycardial pacing (ATP) were evaluated using device reports. Appropriate therapy events were defined as ATP or shock therapies delivered for the treatment of VT and VF. Inappropriate therapy events were defined as ATP or shock therapies

delivered for tachycardia, including atrial fibrillation (AF), supraventricular tachycardias (SVTs), and sinus tachycardia, as well as for device errors, such as oversensing and lead dislodgement. All device therapy events, both appropriate and inappropriate, were classified as therapies. If one patient experienced both appropriate and inappropriate therapy during the follow-up period, the two therapy events were counted separately. If one patient experienced multiple events of appropriate or inappropriate therapy during the follow-up period, each event was counted separately. Mortality was evaluated using medical records and making telephone contact with patients' families. Mortality was classified as cardiac-related and non-cardiac mortality. In the present study, all-cause mortality and cardiac-related mortality were evaluated. LVEF was calculated using biplane Simpson's equation and the apical four-and two-chamber views. Blood samples were analyzed before device implantation.

Cardiac rehabilitation

The CR program was started in the early phase after device implantation. Patients underwent CR a few times a week for 2–6 months. CR consisted of aerobic exercise using a bicycle ergometer. The prescribed intensity of the exercise was determined for each patient individually at 40%–60% of heart rate (HR) reserve (Karvonen's equation ; k = 0.4–0.6), at an anaerobic threshold obtained by cardiopulmonary exercise (CPX) or at Levels 12–13 of the Borg scale for ratings of perceived exertion (RPE) according to the guidelines of the Japanese Circulation Society (JCS)[19].

Exercise capacity was measured by CPX. If patients were physically exhausted or had developed severe dyspnea or dizziness during CPX, the exercise was discontinued. Peak oxygen consumption (VO_2) was defined as maximum exercise load. Resting and maximal HR were measured using a continuous electrocardiogram during CPX testing at the beginning of CR (pre-CR) and at the end of CR (post-CR) throughout the follow-up period. Exercise capacity was evaluated using the results of these CPX tests. The zone for the programmed rate during exercise was determined for each patient by their physician. The exercise intensity for individual patients was determined on the basis of the level of CR. If CPX could not be performed because of a low exercise capacity, the exercise intensity was determined for each individual patient by their cardiologist.

ICD or CRT-D implantation and definitions

Decisions to implant ICDs or CRT-Ds were made with reference to the American College of Cardiology (ACC) / American Heart Association (AHA) / Heart Rhythm Society (HRS) guidelines for device-based therapy of cardiac rhythm abnormalities and the guidelines for non-pharmacotherapy of cardiac arrhythmias published by the Japanese Circulation Society[20, 21]. When CRT-Ds were implanted, the LV lead was implanted transvenously via the coronary sinus tributaries and placed to preferably stimulate the lateral or posterolateral LV wall.

The devices were programmed as follows. If ventricular arrhythmia was confirmed, the rate zone was set after considering the cycle length of tachycardia. If the cycle length of the

ventricular arrhythmia could not be confirmed in patients with a device implanted for primary prevention, the rate zone and the therapies were programmed according to the directions of the attending physician. The standard programming was as follows: the VT zone was defined as a ventricular rate up to 150 b.p.m., and fast VT was defined as a ventricular rate up to 188 b.p.m. The VF zone was defined as a ventricular rate up to 250 b.p.m. The ICDs were programmed as follows: the VT monitor zone was programmed in all patients to 150–188 b.p.m., with an attempt to terminate any VT faster than 188 b.p.m. using ATP or device shocks. Termination of VF faster than 250 b.p.m. was attempted directly using device shocks. The number of intervals to detect the programming rate zone was set to 18 of 24 intervals. ATP was attempted with eight pulses at 88% of the measured cycle length with a 10-ms decrement between bursts. The initial device shock was attempted at the defibrillation threshold plus at least 10 J. The remaining device shocks were maximal energy shocks.

Statistical analysis

Data are presented as the mean ± SD where appropriate, with categorical data summarized as frequencies and percentages. The significance of differences in baseline characteristics between the CR and non-CR groups was analyzed using unpaired Student's t-tests. The Kaplan–Meier method was used to analyze the time to recurrence of the therapy event and mortality during the follow-up period, and compared using the log-rank test. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Data from 222 patients (178 men, 44 women) who were implanted with an ICD or CRT-D were evaluated. Mean patient age was 67 ± 11 years and the baseline characteristics of the patients are summarized in Table 1. Of these 222 patients, 70 (31%) underwent CR and 152 (69%) did not. Patients in the CR group performed CR for mean of 115.6 ± 15.3 days. There was no statistically significant difference in baseline age, sex, body mass index, LVEF, or primary prevention between the two groups. In addition, there was no significant difference between the two groups with regard to single / dual chamber involvement, although patients in the CR group were more likely to have a CRT-D than those in non-CR group (59% vs 43%, respectively; $P = 0.03$). There were no significant differences in underlying disease at baseline, in the history of AF (32% vs 34%), or in baseline medications, except for diuretics (90% vs 78%; $P = 0.03$), between the CR and non-CR groups (Table 1).

Comparison of mortality and therapy events between the CR and non-CR groups

Comparisons of mortality and therapy events between the CR and non-CR groups are summarized in Table 2. During the 12-month follow-up, eight patients (11.4%) in the CR group and 26 (17.0%) patients in the non-CR group died from any cause ($P = 0.28$), with five (7.1%) and 15 (9.8%) cardiac-related deaths in the CR and non-CR groups, respectively ($P = 0.49$).

Table 1 Comparison of baseline characteristics in the entire study population and in patients undergoing cardiac rehabilitation (CR) or not (non-CR)

	Total population (n = 222)	CR group (n = 70)	Non-CR group (n = 152)	*P*-value
Age (years)	67 ± 11	69 ± 11	66 ± 11	0.16
No. males	178 (80%)	60 (85%)	119 (78%)	0.21
BMI (kg/m^2)	23 ± 4	22 ± 6	23 ± 5	0.52
Resting HR (b.p.m.)	74.1	74.1	74.1	0.98
SBP/DBP (mmHg)	111.5/64.5	109.0/63.5	112.6/64.9	0.08/0.36
LVEF (%)	29 ± 8	28 ± 7	30 ± 8	0.14
NYHA Class Ⅲ / Ⅳ	94 (42%)	36 (51%)	58 (38%)	0.08
Primary prevention	118 (53%)	40 (57%)	78 (51%)	0.38
Device				
Single chamber	40 (18%)	10 (14%)	30 (20%)	0.33
Dual chamber	75 (34%)	19 (27%)	56 (37%)	0.13
CRT	107 (48%)	41 (59%)	66 (43%)	0.03
Underling disease				
Ischemic heart disease	95 (44%)	30 (44%)	65 (43%)	0.98
Hypertension	123 (55%)	40 (56%)	83 (53%)	0.77
Diabetes mellitus	82 (37%)	28 (40%)	54 (36%)	0.55
Hyperlipidemia	128 (58%)	41 (59%)	87 (57%)	0.88
CKD	93 (42%)	30 (44%)	63 (41%)	0.88
Atrial fibrillation[A]	72 (32%)	21 (32%)	51 (34%)	0.86
Medication				
ACE-I/ARB	134 (62%)	44 (64%)	91 (61%)	0.76
Beta-blockers	173 (78%)	58 (83%)	115 (76%)	0.28
Amiodarone/sotalol	67 (30%)	18 (26%)	49 (32%)	0.35
Digoxin	14 (6%)	4 (6%)	10 (7%)	0.99
Diuretics	181 (82%)	63 (90%)	118 (78%)	0.03
Laboratory data				
K (mEq/l)	4.2 ± 0.55	4.4 ± 0.54	4.3 ± 0.57	0.22
Creatinine (mg/dl)	1.5 ± 1.7	1.2 ± 1.0	1.6 ± 1.4	0.19
BNP (pg/ml)	713 ± 1080	570 ± 520	794 ± 1292	0.20

Data are given as the mean ± SD or as n (%), as appropriate.

[A]The definition of "atrial fibrillation" (AF) included paroxysmal, persistent, and chronic AF.

ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

There was a significant difference in all device therapy events between the CR and non-CR groups (7.1% vs 20.2%; $P = 0.01$). During the 12-month follow-up, four (5.7%) patients in the CR group and 20 (13.1%) patients in the non-CR group experienced first appropriate ICD therapy ($P = 0.09$). There were significantly fewer inappropriate therapy events in the CR compared with non-CR group (1.4% vs 9.2%, respectively; $P = 0.03$).

Table 2 Mortality and therapy events during the follow-up period in patients undergoing cardiac rehabilitation (CR) or not (non-CR)

	CR group (n = 70)	Non-CR group (n = 152)	*P*-value
All-cause mortality	8 (11.4%)	26 (17.0%)	0.28
Cardiac mortality	5 (7.1%)	15 (9.8%)	0.49
All device therapy events	5 (7.1%)	31 (20.2%)	0.01
Appropriate therapy events	4 (5.7%)	20 (13.1%)	0.09
Inappropriate therapy events	1 (1.4%)	14 (9.2%)	0.03

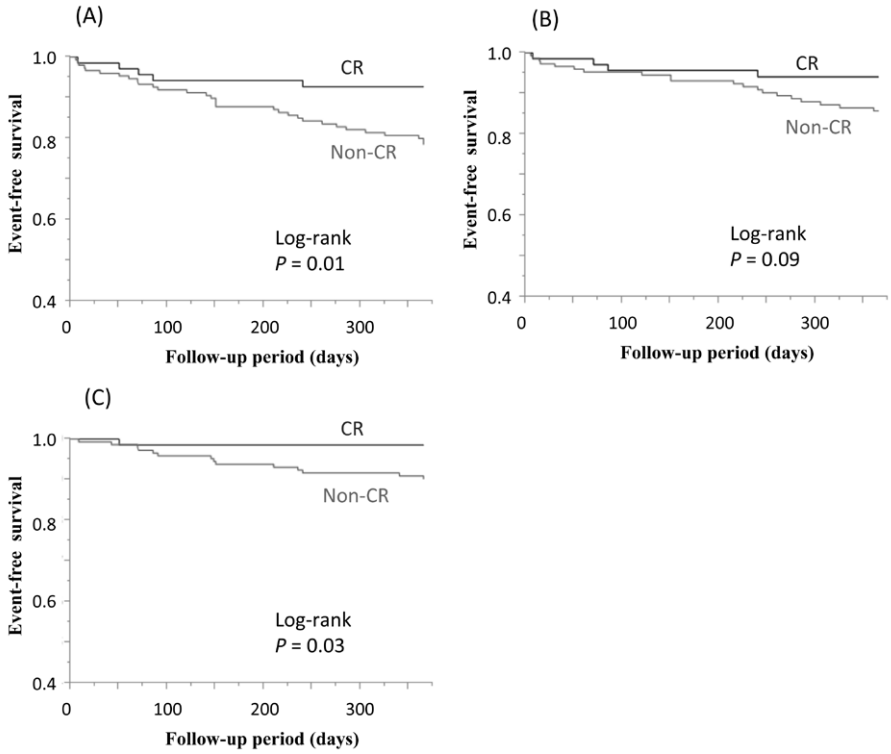

Fig. 1. Kaplan–Meier estimates of the percentage of patients (n = 222) remaining free from (A) all device therapies, (B) appropriate therapy, and (C) inappropriate therapy during the follow-up period. The follow-up period started from the day of implantable cardioverter defibrillator (ICD) implantation. The event-free rates in patients undergoing cardiac rehabilitation (CR) or not (non-CR) were as follows: (A) for all device therapies, 93% and 80%, respectively, with a 13% risk reduction in the CR group; (B) for appropriate therapy, 94% and 87%, respectively, with a 7% risk reduction in the CR group; and (C) for inappropriate therapy, 99% and 91%, respectively, with an 8% risk reduction in the CR group. and 4 mg thiotriazinone as an impurity (right line of panels).

Fig. 1A shows the Kaplan–Meier estimates of the percentage of patients remaining free from all device therapy (n = 222) during the 12-month follow-up period. The event-free rate during the follow-up period was 93% in the CR group and 80% in the non-CR group. The risk reduction in the CR group was 13% (log-rank $P = 0.01$).

Fig. 1B shows the Kaplan–Meier estimates of the percentage of patients remaining free from appropriate therapy (n = 222) during the 12-month follow-up period. The event-free rates in

the CR and non-CR groups during the follow-up period were 94% and 87%, respectively. The risk reduction in the CR group was 7% (log-rank $P = 0.09$).

Fig. 1C shows the Kaplan–Meier estimates of the percentage of patients remaining free from inappropriate therapy (n = 222) during the 12-month follow-up period. The event-free rates in the CR and non-CR groups during the follow-up period were 99% and 91%, respectively. The risk reduction in the CR group was 8% (log-rank $P = 0.03$).

Fig. 2A shows the Kaplan–Meier estimates of the percentage of patients remaining free from all-cause mortality (n = 222) during the 12-month follow-up period. The event-free rate during the follow-up period was 89% in the CR group and 83% in the non-CR group (log-rank $P = 0.28$).

Fig. 2B shows the Kaplan–Meier estimates of the percentage of patients remaining free from cardiac mortality (n = 222) during the 12-month follow-up period. The event-free rates in the CR and non-CR groups during the follow-up period were 93% and 90%, respectively (log-rank $P = 0.49$).

Details of the inappropriate therapy events are given in Table 3. SVT in the present study was defined as AF, atrial flutter, and atrial tachycardia. In the CR and non-CR groups, one and four patients, respectively, experienced inappropriate therapy because of sinus tachycardia. In addition, in the non-CR group, another eight patients experienced inappropriate therapy because of SVT and two patients received inappropriate therapy because of oversensing. The causes of inappropriate therapy in the non-CR group were investigated. With regard to inappropriate therapy events because of SVT, seven were due to AF (four patients with a CRT-D, one patient with an ICD) and the remaining event was due to suspected atrial tachycardia in one patient with a CRT-D. All four patients who received inappropriate therapy, because of sinus tachycardia, had an ICD, whereas of the two patients who received inappropriate therapy as a result of oversensing, one had a CRT-D and the other had an ICD.

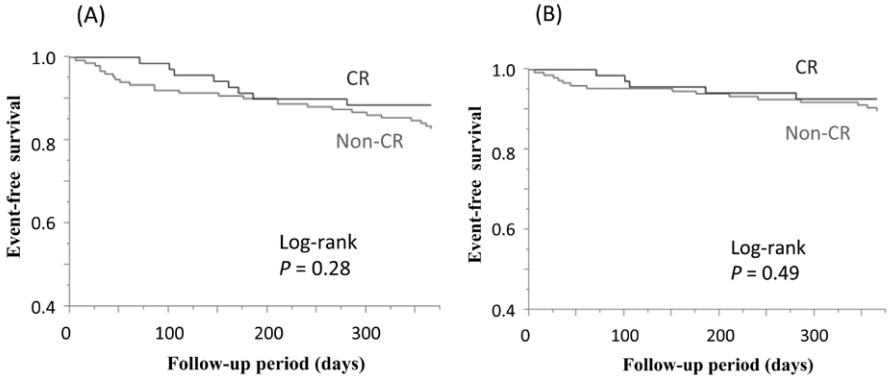

Fig. 2. Kaplan–Meier estimates of the percentage of patients (n = 222) remaining free from (A) all-cause mortality and (B) cardiac-related deaths during the follow-up period. The follow-up period started from the day of implantable cardioverter defibrillator (ICD) implantation. The event-free rates in patients undergoing cardiac rehabilitation (CR) or not (non-CR) were as follows: (A) for all-cause mortality, 89% and 83%, respectively, with a 6% risk reduction in the CR group; and (B) for cardiac-related deaths, 93% and 90% respectively, with a 3% risk reduction in the CR group.

Changes in baseline characteristics and CPX data pre-and post-CR

Changes in baseline characteristics pre-and post-CR in the CR group are summarized in Table 4. Twenty-two patients performed a CPX test pre-and post-CR. There was no significant difference in resting HR, peak HR, or RPE between these two groups. However, peak VO_2 was significantly higher post-CR compared with pre-CR (14.0 vs 12.9 ml / kg per min, respectively ; $P = 0.005$) .

Discussion

Main findings

The main finding of the present study is that there were fewer inappropriate therapy events in the CR than in the non-CR group during the 12-month follow-up period. However, the number of appropriate therapy events, cardiac mortality, and all-cause mortality were similar between the two groups. Furthermore, peak VO_2 improved in patients in the CR group after CPX. At baseline, the proportion of patients implanted with a CRT-D and diuretic use were higher in the CR than non-CR group.

Table 3 Details of inappropriate therapy events in patients undergoing cardiac rehabilitation (CR) or not (non-CR)

	CR group (n = 70)	Non-CR group (n = 152)	Total study population (n = 222)
Sinus tachycardia	1	4	5
SVT[A]	0	8	8
Oversensing	0	2	2
Total	1	14	15

Data show the number of patients in each group.

[A]Supraventricular tachycardia (SVT) includes atrial fibrillation, atrial flutter, and atrial tachycardia.

Table 4 Characteristics before and after cardiac rehabilitation (CR) as evaluated in cardiopulmonary exercise tests

	Pre-CR (n = 22)	Post-CR (n = 22)	*P*-value
Resting HR (b.p.m.)	75.7 ± 14.1	73.7 ± 7.6	0.45
Peak HR (b.p.m.)	118.5 ± 16.4	121.2 ± 17.4	0.35
Peak VO_2 (ml/kg per min)	12.9 ± 3.0	14.0 ± 3.0	0.005
RPE (leg)	15.0 ± 2.0	15.5 ± 2.3	0.49
RPE (dyspnea)	16.1 ± 2.4	16.1 ± 3.2	1.00

Data are given as the mean ± SD.

HR, heart rate ; VO_2, oxygen consumption ; RPE, Borg scale for rating of perceived exertion.

Association between CR and ICD or CRT-D implantation

Some studies have reported an improved prognosis for patients with chronic heart disease or ischemic heart disease after CR[14-18].

Recently, it has been reported in some studies that CR does not increase the risk of inappropriate shocks[22-25]. The findings of the present study indicate that CR in patients implanted with an ICD or CRT-D does not induce inappropriate therapy events. Furthermore, CR reduces the number of shocks for patients. We believe that the improvement in exercise capacity after CR may explain these results.

In the present study, almost all inappropriate therapy events were related to sinus tachycardia and arrhythmia (Table 3). Inappropriate therapy events such as device errors, including oversensing, were confirmed in only two patients in the present study. Therefore, a rate control strategy may lead to a reduction in the incidence of inappropriate therapy. In general, the rate control strategy in the present study relied on the use of beta-blockers and anti-arrhythmic drugs, such as amiodarone and sotalol. Both medication and CR reduced the HR of patients. If patients improve their exercise capacity, the increase in HR on exercise would be relatively smaller compared with patients in whom there has been no improvement in exercise capacity[26]. Improvements in exercise capacity may suppress the elevation in HR, and may protect patients against inappropriate therapy events.

Association between inappropriate therapy and mortality

The findings of the present study indicate that CR reduces the number of therapy events, but CR did not reduce the number of deaths due to any cause. Subanalysis of MADIT Ⅱ data[8] supports the findings of the present study. Inappropriate shock was associated with the risk of all-cause mortality, but inappropriate therapy, including shock and ATP, did not significantly affect mortality. Furthermore, the subanalysis of the MADIT Ⅱ data suggested that inappropriate ATP may not affect mortality[8]. The results of the present study are consistent with those of the MADIT Ⅱ subanalysis in that CR reduced inappropriate therapy events (including shock and ATP), but did not reduce mortality.

The findings of the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients Ⅲ (ADVANCE Ⅲ) trial[10, 11] also support the findings of the present study. Specifically, that the trial indicated that programming long detection intervals reduced the number of inappropriate shocks, but did not reduce mortality[10, 11].

We speculate that follow-up period is important to clearly demonstrate the association between inappropriate therapy and mortality. In the MADIT Ⅱ and SCD-HeFT trials, patients were followed for a median 20 and 45 months, respectively[8, 9], compared with only 12 months in the present study. If the follow-up period had been longer in the present study, a significant association may have been found between inappropriate therapy and mortality.

Study limitations

The present study has some limitations. First, only patients in the CR group received CPX

instruction. Exercise capacity and maximum oxygen intake were not evaluated in patients in the non-CR group. Furthermore, only CPX was used to investigate the effects of CR. CPX requires patients to have some exercise capacity, and if patients could not undertake CPX because of low exercise capacity, the effects of CR were not investigated. Second, the present study was performed on a small number of patients. Thus, the results should be interpreted with caution. However, we believe that the statistical methodology was rigorous, and CR and inappropriate therapy were well validated, which substantiates the main conclusions. Third, in some patients the cycle length of the VT / VF zone and exercise intensity were determined at the discretion of individual physicians. It is possible that this could have led to the setting of inappropriate rate zones, and overwork may have led to excessive elevation of HR. It would have been better if, in the present study, the definition of the rate zone was clearer. Further prospective studies are needed to evaluate the relationship between CR and device therapies.

Conclusion

The present study suggests that improvement in exercise capacity as a result of CR may reduce the number of therapy events, especially inappropriate therapy events, in patients with an implanted ICD or CRT-D. An improvement in exercise capacity may be the main reason for the reduction in the number of therapy events.

Conflict of interest

The authors have declared no conflict of interest.

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