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Cardiac resynchronization therapy to prevent life-threatening arrhythmias in patients with congestive heart failure

Takashi Kurita, MD, PhD,[a,*] Takashi Noda, MD, PhD,[b] Takeshi Aiba, MD, PhD,[b] Ikutaro Nakajima, MD,[b] Wataru Shimizu, MD, PhD,[b] Koichiro Motoki, MD, PhD,[a] Ryobun Yasuoka, MD, PhD,[a] Shunichi Miyazaki, MD, PhD,[a] Shiro Kamakura, MD, PhD[b]

[a]*Department of Medicine, Division of Cardiology, Faculty of Medicine, Kinki University, Osaka, Japan*
[b]*Division of Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan*

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Abstract Various clinical data demonstrate that cardiac resynchronization therapy (CRT) provides a favorable structural as well as electrical remodeling. The CArdiac Resynchronization–Heart Failure study, which tested the pure effect of CRT (using CRT devices without the capability of defibrillation) clearly showed a significant reduction in the total mortality by partly preventing sudden cardiac death. The antiarrhythmic effects of CRT are explained, at least in part, by ionic and genetic modulation of ventricular myocytes. It has been revealed in animal experiments to mimic disorganized ventricular contraction that CRT reverses down-regulation of certain K^+ channels and abnormal Ca^{2+} homeostasis in the failing heart. However, CRT can be proarrhythmic in some particular cases especially in the early phase of this therapy. According to our study, proarrhythmic effects after CRT can be observed in approximately 10% of patients. The relatively high incidence of the proarrhythmic effects of CRT may promote a trend toward selecting CRT-D rather than CRT-P.

Keywords: Cardiac resynchronization therapy; Ventricular tachyarrhythmia; Heart failure; Proarrhythmic effect; Antiarrhythmic effect

Introduction

Various clinical data demonstrate that cardiac resynchronization therapy (CRT) provides a favorable structural as well as electrical remodeling.[1-5] The CArdiac Resynchronization–Heart Failure (CARE-HF) study, which tested the pure effect of CRT (using CRT devices without the capability of defibrillation) clearly showed a significant reduction in the total mortality by partly preventing sudden cardiac death (SCD).[5,6] The antiarrhythmic effects of CRT are attributable to reversal of structural and electrical remodeling of the left ventricle (LV) in association of heart failure toward the creation of substrates for reentry of excitation.

However, epicardial LV pacing can also be proarrhythmic through an induction of heterogeneous ventricular depolarization and repolarization resulting from nonphysiological propagation of excitation.[7-9] In the present article, we discuss such a dual potential of CRT toward prevention and promotion of arrhythmias.

Proarrhythmic effects of CRT

Fig. 1 shows a representative case in whom the proarrhytmic effects of CRT were highly suspected. This patient had a long history (>20 years) of heart failure and complete left bundle branch block (CLBBB) without any significant ventricular arrhythmias. The first VF episode developed only 6 days after implantation of CRT-P, giving us a warning against a proarrhythmic risk of CRT even in patients without history of serious ventricular arrhythmias.

Our study

We investigated "early development of lethal arrhythmic events after CRT."[10] The condition of patients enrolled was defined as follows: (1) no previous episodes of sustained VT/VF or syncope before the CRT implantation, (2) new development of sustained VT/VF, SCD, or appropriate shocks delivered by a CRT-D within 6 months after implantation of CRT. Fifty-one consecutive patients

* Corresponding author. Department of Medicine, Division of Cardiology, Faculty of Medicine, Kinki University, 377-2 Ohono-Higashi, Osaka-Sayama, Osaka 589-8511, Japan.
E-mail address: kuritat@med.kindai.ac.jp

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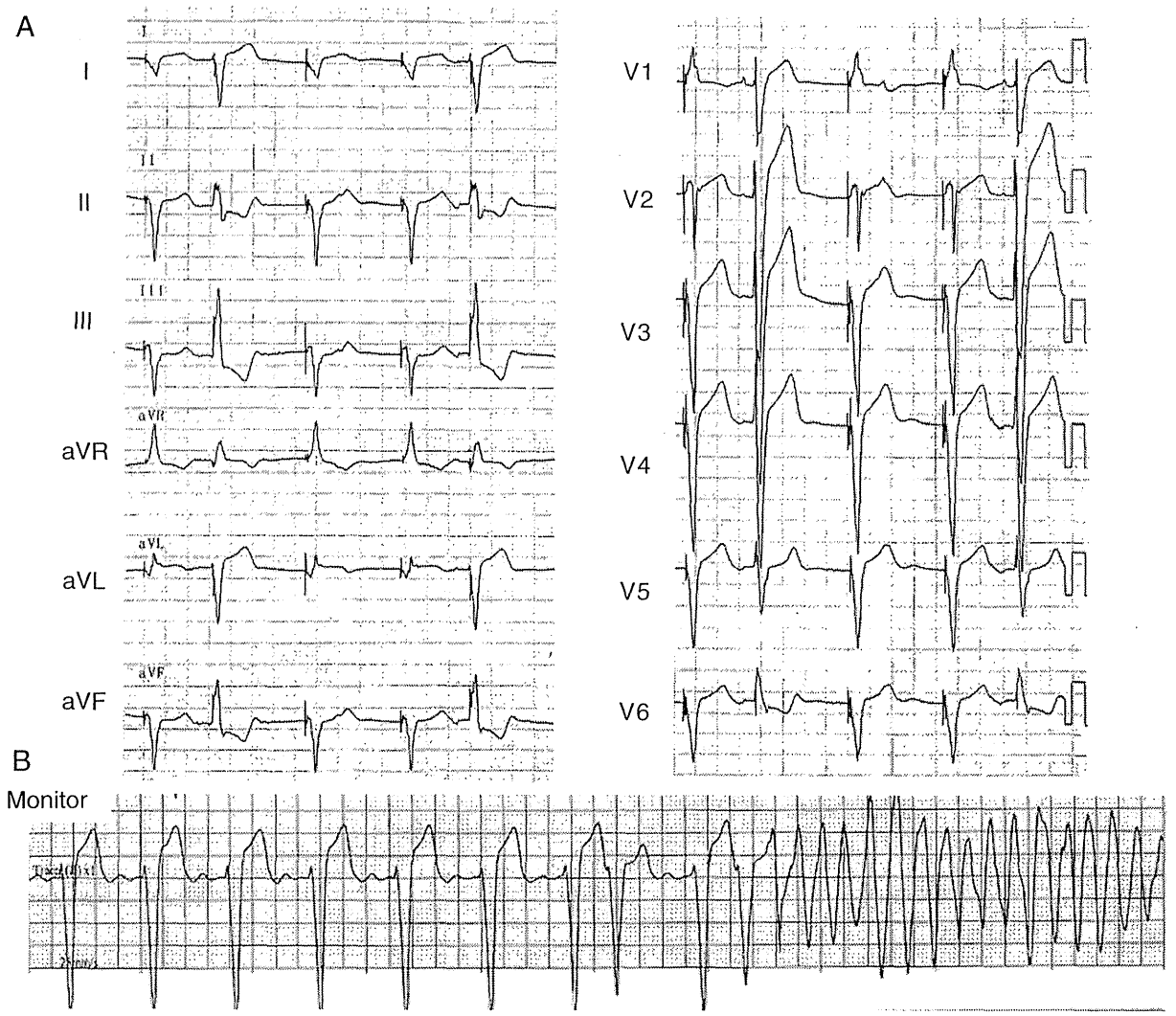

Fig. 1. A case with newly development of VF 6 days after implantation of CRT pacemaker (CRT-P). A, CRT-P was implanted in heart failure patient with CLBBB and permanent AF. Because of AF, occasional conducted QRS complexes with CLBBB configuration are seen. B, This patient had a long history (>20 years) of heart failure and CLBBB without any significant ventricular arrhythmias. The patient showed the first VF episode only 6 days after implantation of CRT-P, giving us a warning against a proarrhythmic risk of CRT.

who underwent CRT were included in this study. We excluded the patients who had a worse New York Heart Association (NYHA) functional class after the CRT and who had VT episodes that were terminated only by antitachycardia pacing. The early development of lethal arrhythmic events after the CRT was observed in 6 (11.7%) of 51 patients. They were divided into 2 groups according to the presence of early phase events: a group with events (group E, n = 6) and a group without events (group non-E, n = 45), and we compared several clinical parameters such as the baseline NYHA functional class, response to CRT (responder or nonresponder), underlying heart disease, antiarrhythmic drug usage, and preexisting arrhythmias (atrial fibrillation [AF] and nonsustained VT [NSVT]) between the 2 groups. There was no significant difference between the 2 groups for all the parameters except for preexisting arrhythmias. Preexisting AF and NSVT of 5 bursts or more were observed more frequently in group E than group non-E (6/6 vs 20/45, $P < .01$ and 6/6 vs 17/45, $P < .01$, respectively, Fig. 2). These observations suggest that preexisting AF and NSVT may be important predictors for the proarrhythmic risk of CRT implantation regardless of the hemodynamic response of the subjects.

Mechanism of the proarrhythmic effects of CRT

The transvenous insertion of an LV lead into a cardiac vein on the epicardial surface of the heart is an essential technique to obtain safe and stable long-term LV pacing.[11] This technique produces nonphysiological propagation of the excitation from the epicardium to endocardium and may lead to an increase in the dispersion of the repolarization because the epicardial ventricular muscle having shorter action potential duration (APD) is excited earlier than the endocardial ventricular muscle having longer APD. This

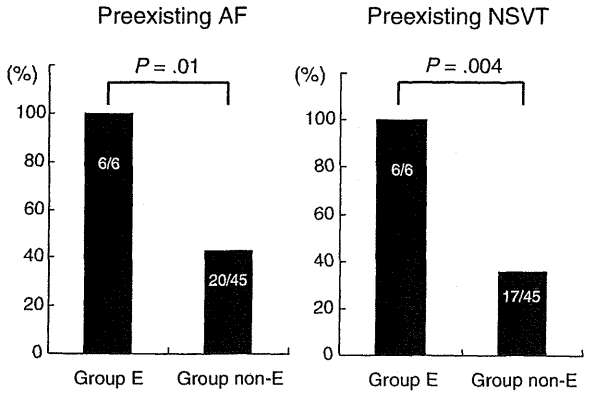

Fig. 2. Preexisting arrhythmias in the patients with (group E) and those without (group non-E) early development of lethal arrhythmic events after CRT. Preexisting AF and NSVT were observed more frequently in group E than group non-E (6/6 vs 19/45, $P < .01$, and 6/6 vs 17/45, $P < .01$, respectively).

may set a sage for reentry of excitation causing VT/VF. Spatially heterogenous prolongation of APD in the ventricle of failing hearts may further facilitate the initiation and perpetuation of reentrant arrhythmias.[12,13]

Right ventricular (RV) pacing induces a significant LBBB pattern and sometimes leads to the deterioration in the LV function. Upgrading from a traditional RV pacemaker to a biventricular (Bi-V) pacemaker is highly recommended for patients with a reduced cardiac function and atrioventricular (AV) block (block).[14]

Recently, an intriguing case of idiopathic dilated cardiomyopathy with heart failure and complete AV block was reported by Ikutomi et al,[15] where upgrading from the preexisting VDD pacemaker to CRT-D resulted in a significant proarrhythmia. Upgrading from the preexisting VDD pacemaker to CRT-D was performed aiming to improve the heart failure. A marked QT prolongation and torsade de pointes (TdP) occurred immediately after switching from RV pacing to LV or Bi-V pacing. Several weeks later, however, Bi-V pacing caused only moderate QT prolongation without TdP induction. The Bi-V pacing was able to be continued thereafter, and QT interval shortened gradually in association with improvement of heart failure. It is suggested from this report that proarrhythmic risk of Bi-V pacing is most remarkable in the early phase of CRT, and it may decrease in the remote phase probably through a reversal of (or adaptation to) the electrical remodeling of the heart.

Another mechanism of proarrhythmia with CRT is relevant to preexisting anatomical structure in favor of reentry. We experienced a case of nonischemic dilated cardiomyopathy (65 year old man) with heart failure, complete AV block and permanent AF. ICD had been implanted for the treatment of monomorphic sustained VT. During a 3-year follow-up period, the patient experienced sporadic electrical therapies, but his heart failure condition deteriorated gradually to NYHA III/IV. We, therefore, decided to upgrade from ICD to CRT-D. A CRT-D was implanted through thoracotomy. He responded well to CRT-D, giving rise to an improvement of NYHA class from III/IV to II. One month later, however, he was admitted in the emergency department of our hospital because of frequent episodes of sustained monomorphic VT (an electrical storm). The VT was terminated repeatedly by antitachycardia pacing (Fig. 3A). There were no other factors of proarrhythmia (such as worsening of heart failure or electrolyte imbalance) than Bi-V pacing. After switching from Bi-V to RV pacing, the electrical storm terminated immediately (Fig. 3B). When the pacing turned back to Bi-V pacing, the electrical storm reappeared right away (Fig. 3B). The proarrhythmia of Bi-V pacing in this patient could be explained by an entrance of wave front from LV pacing site into preexisting reentry circuits. Anisotropic fiber orientation in the LV myocardium or summation of depolarizing waves is considered to be involved in such events favoring the electrical storm.[16,17]

Future device

Advanced technology using transseptal (transmitral) lead approach will provide safe and stable endocardia LV pacing in near future.[18] This technique will resolve proarrhythmic issues of epicardial approach by producing more physiological propagation of depolarization through LV, and it will also allow us to implant the LV lead regardless of cardiac vein anatomy.

Antiarrhythmic effects of CRT

CRT is expected to prevent life-threatening ventricular arrhythmias in the failing heart because the procedure would cause a reversal of structural and electrical remodeling, favoring reentry of excitation.[1-7] Tanabe et al[19] reported the apparent antiarrhythmic effect of CRT in a patient with idiopathic dilated cardiomyopathy who experienced an electrical storm (frequent monomorphic sustained VT) after implantation of ICD. They performed an acute study with Bi-V pacing before the CRT-D implantation and confirmed an immediate improvement in the systemic hypotension and degree of mitral regurgitation during the Bi-V pacing. Application of CRT to this patient resulted in an immediate hemodynamic improvement in association with complete elimination of the electrical storm, which had been resistant to pharmacological therapies.

An analysis of the combined InSync-ICD and Contact-CD patients demonstrated that CRT was associated with no significant change in the incidence of polymorphic VT or monomorphic VT.[20] However, other reports showed data revealing that the incidence of malignant VT was reduced following CRT.[19,21-23] Based on these results, CRT has favorable or at least no harmful effects on substrates for VT/VF in heart failure patients.

As previously mentioned, the CARE-HF study demonstrated a significant improvement in the SCD rate.[6] However, in that trial, the survival curves showing the freedom from all causes of death in the control and CRT group began to separate approximately 200 days after the randomization. On the other hand, the survival curves of SCD started to separate after approximately 700 days. The

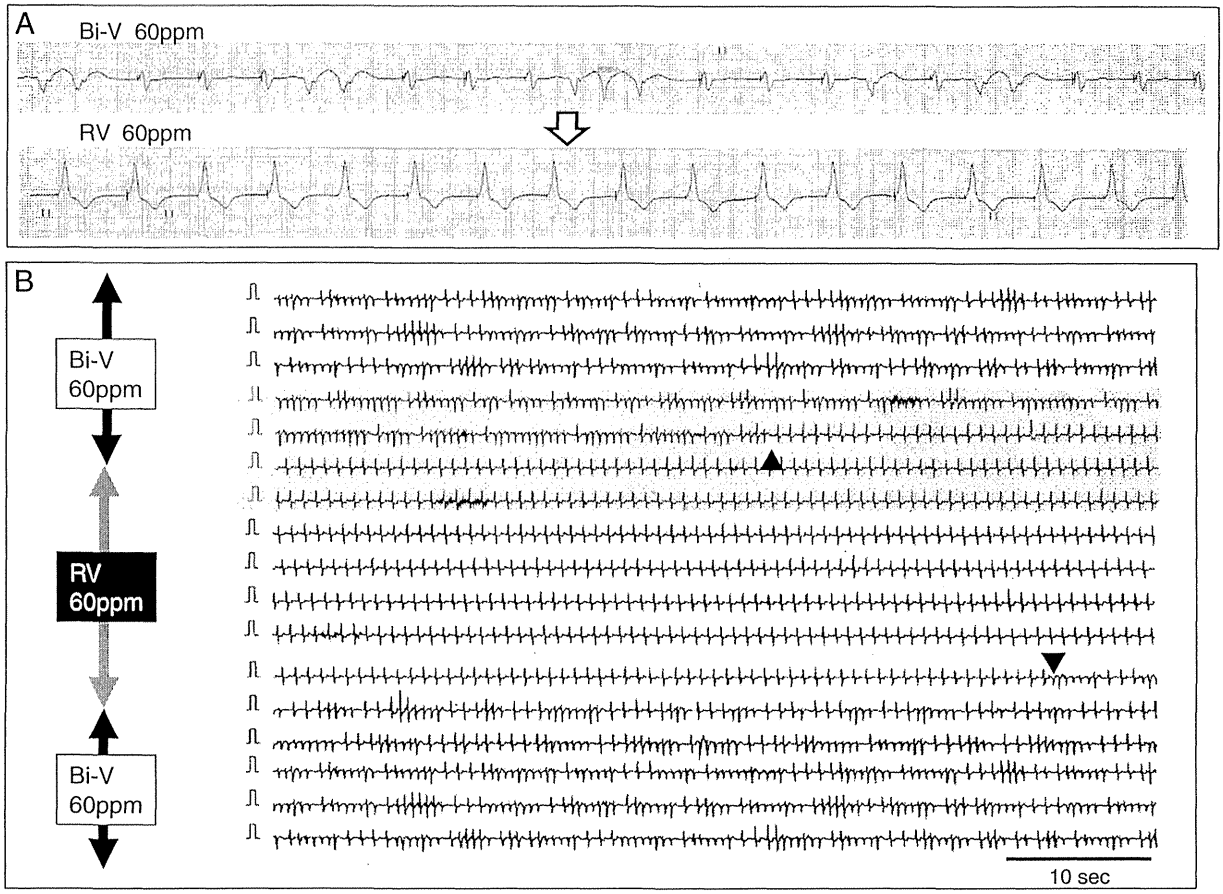

Fig. 3. Proarrhythmic effects of CRT in a patient of dilated cardiomyopathy (65-year-old man) with heart failure, complete AV block, and permanent AF. ICD had been implanted for the treatment of monomorphic sustained VT. Because of deterioration of heart failure, we upgraded from ICD to CRT-D. He responded well to CRT, giving rise to improvement of NYHA classes. One month later, however, he was experienced frequent episodes of sustained monomorphic VT, which were terminated repeated by antitachycardia pacing (A). After switching from Bi-V to RV pacing, the electrical storm terminated immediately (B, upward arrowhead). When the pacing turned back to Bi-V, the electrical storm reappeared right away (B, downward arrowhead). ppm indicates pacing per minute, RV, right ventricular pacing.

antiarrhythmic effect of CRT to prevent SCD might require sufficient time for reversal of structural and electrical remodeling of the heart, although this interpretation remains to be substantiated.

Effects on AF

The incidence of AF increases with an advancing NHYA cardiac functional class.[24,25] The contribution of the atrial contraction to the cardiac performance in a normal heart is considered to be small. However, the development of AF in a failing heart significantly affects the cardiac dysfunction by diminishing the atrial kick (AV synchrony). Inappropriate rapid ventricular rate with irregular R-R intervals may also contribute the cardiac dysfunction.[26-28]

Optimization of the left AV conduction delay and a simultaneous contraction of the entire LV reduces the LV end-diastolic pressure, leading to a reduction of wall stress in the LV and LA in favor or termination and prevention of AF. We experienced 2 cases in whom long-lasting AF was terminated and sinus rhythm has been maintained thereafter. Because we did not expect the termination of the AF after the CRT, we did not implant an atrial lead. In cases with unexpected restoration of sinus rhythm as in this patient, Bi-V pacing with the VVI mode may provoke pacemaker syndrome. We need to lean certain parameters predicting conversion from AF to sinus rhythm after CRT implantation.

Delnoy et al[29] reported their experience in 96 CRT patients with permanent or persistent AF. They implanted atrial leads in patients with AF lasting less than 2 years and followed them up for 2 years. Antiarrhythmic drug therapy (mainly amiodarone) was used after CRT implantation to resume or to preserve sinus rhythm. In that study, 25% of 96 AF patients were in sinus rhythm after 1 year. Eight patients received cardioversion at the time of the implant, whereas 16 patients reverted to sinus rhythm spontaneously. At 2 years, 21% of the AF group was in sinus rhythm. This study suggests that amiodarone treatment after cardioversion is promising in CRT patients with AF for resumption and preservation of sinus rhythm. They recommended that the implantation of an atrial lead may have merit in CRT patients with AF lasting less than 2 years. AV synchrony obtained by an atrial lead may dramatically improve the

heart failure, but in the case of those without a lead, reversion to sinus rhythm may provoke pacemaker syndrome and an insufficient improvement.

Genetic aspects of reverse electrical remodeling

The electrophysiologic hallmark of cells and tissue isolated from failing hearts is the prolongation of the APD and a conduction delay.[30,31] In human studies and a number of animal models of heart failure, functional down-regulation of K^+ currents and alterations in depolarizing Na^+ and Ca^{2+} currents and transporters are demonstrated. In experiments on dog of heart failure induced by dyssynchronous LV contraction (DHF), Aiba et al[12] and Aiba and Tomaselli[13] have shown that CRT partially restores DHF-induced ion channel remodeling and abnormal Ca^{2+} homoeostasis and attenuates the regional heterogeneity of APD. CRT was also shown to improve β-adrenergic responsiveness of Ca^{2+} handling in the DHF model. Such electrophysiological changes induced by CRT may suppress ventricular arrhythmias favoring a better survival.[32]

Conclusions

CRT can be proarrhythmic in some particular cases especially in the early phase of this therapy until electrical reverse remodeling has become established. According to our study, proarrhythmic effects after CRT can be observed in approximately 10% of patients. The relatively high incidence of the proarrhythmic effects of CRT may promote a trend toward selecting CRT-D rather than CRT-P.

Indeed, CRT can be antiarryhthmic. Even in the early phase after beginning CRT, it immediately improves the hemodynamic situation. A decrease of the LV endodiastolic pressure would ameliorate the stretch-induced arrhythmogenic alterations of ionic currents. In patients who ideally respond to CRT, it creates structural reverse remodeling accompanied by electrical reverse remodeling in the remote phase. Once such a striking reverse remodeling has been established, CRT acts as a potent antiarrhythmic treatment thereafter.

The antiarrhtymic effects of CRT have come to be explained by the viewpoint of the ionic and genetic regulation of the myocytes.

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Original Article

Effects of cardiac resynchronization therapy in patients with inotrope-dependent class IV end-stage heart failure

Ikutaro Nakajima, MD[a], Takashi Noda, MD, PhD[a,*], Hideaki Kanzaki, MD[a], Kohei Ishibashi, MD[a], Koji Miyamoto, MD[a], Yuko Yamada, MD[a], Hideo Okamura, MD[a], Kazuhiro Satomi, MD, PhD[a], Takeshi Aiba, MD, PhD[a], Shiro Kamakura, MD, PhD[a], Toshihisa Anzai, MD, PhD[a], Masaharu Ishihara, MD, PhD[a], Satoshi Yasuda, MD, PhD[a], Hisao Ogawa, MD, PhD[a,b], Wataru Shimizu, MD, PhD[a,c]

[a] Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan
[b] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Japan
[c] Department of Cardiovascular Medicine, Nippon Medical School, Japan

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has been widely used for the treatment of refractory heart failure (HF). However, the efficacy of CRT is not well established in class IV HF patients on inotropic support.

Methods: Twenty-six patients (age 55 ± 18 years, 73% men) with inotrope-dependent HF were reviewed to evaluate the effectiveness of CRT in class IV HF patients on inotropic support.

Results: Intravenous inotropic therapy was administered for 72 ± 56 days before CRT and consisted of dobutamine (n=24; 3.0 ± 1.2 μg kg^{-1} min^{-1}), dopamine (n=2; 4.5 ± 2.1 μg kg^{-1} min^{-1}), and/or milrinone (n=16; 0.12 ± 0.09 μg kg^{-1} min^{-1}). CRT did not produce significant reverse remodeling in eligible patients (left ventricular ejection fraction 23 ± 7% to 25 ± 9%; p=0.23, left ventricular end-diastolic diameter 70 ± 9 mm to 68 ± 9 mm; p=0.14). After CRT device implantation, 13 (50%) patients experienced 1 or more episodes of ventricular tachyarrhythmia or sudden cardiac death. Twenty (77%) patients survived to hospital discharge with weaning from inotropic support (70 ± 70 days after CRT implantation). The 1-year survival rate was 81%. However, data from long-term follow-up showed that 68% of the study patients who attained survival discharge had an HF hospitalization event within the follow-up period.

Conclusion: CRT did not result in significant reverse remodeling in patients with inotrope-dependent class IV end-stage HF. However, it contributed to dramatically improve the cardiovascular outcomes at least in the short-term period in some patients.

1. Introduction

Patients with inotrope-dependent class IV end-stage heart failure (HF) have an extremely poor prognosis with medical therapy alone [1]. For these patients, cardiac transplantation or left ventricular assist device (LVAD) implantation is a suitable option to improve the morbidity and mortality rates. However, because of poor number of donors, legal issues, or financial cost, these therapies could not be used widely especially in non-Western countries.

A significant proportion of HF patients with depressed left ventricular ejection fraction (LVEF) has abnormal electrical activation that is associated with cardiac dyssynchrony. Biventricular pacing has been shown to improve the prognosis of these patients [2]. Recent clinical evidences have shown that cardiac resynchronization therapy (CRT) has made remarkable progress for patients with HF [3–5].

According to a previous report [6], even in patients with New York Heart Association (NYHA) class IV HF, CRT significantly improves mortality and hospitalization rates. However, hemodynamically unstable severe HF patients who require inotropes are usually excluded from major CRT trials, and the current guidelines do not recommend CRT as a therapeutic option for such patients [7,8]. Accordingly, there are limited data about CRT implantation in class IV HF patients on continuous inotropic support, and the efficacy of CRT for such patients is not well established.

2. Methods

2.1. Study population

The population of this retrospective review study comprised consecutive patients implanted with a CRT device between April

* Correspondence to: 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan.
Tel.: +81 6 6833 5012; fax: +81 6 6872 7486.
E-mail address: tnoda@hsp.ncvc.go.jp (T. Noda).

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2004 and April 2011 in the National Cerebral and Cardiovascular Center in Japan. We excluded patients who could not be followed-up for at least 2 years for reasons besides death or LVAD implantation, in order to evaluate the long-term prognosis. The indications for CRT implantation in this population were based on the international standard guidelines [7,8], which include LV systolic dysfunction (LVEF $<35\%$), advanced HF (NYHA class >2), and wide QRS complex (>120 ms) after optimal medical therapy. Among our cohort, we identified 26 consecutive patients with NYHA class IV HF on inotropic support (age 55 ± 18 years, 73% men) who underwent CRT implantation. Clinical characteristics and evaluation variables, including blood tests, 12-lead electrocardiogram, and echocardiography, were recorded at baseline and at all follow-up visits after CRT implantation. This study complies with the Declaration of Helsinki and was approved by the local ethics committee.

2.2. Definition of inotrope dependence

We defined inotrope dependence as the inability to stop or decrease the dose of the inotropes without hypotension, oliguria (<400 mL/day), and/or hypoxia [9]. We excluded patients who required perioperative inotropes within 4 weeks owing to inotrope dependence and a decompensated state of HF. The inotropes used included dobutamine, dopamine, and milrinone. All eligible patients were admitted non-electively, required intravenous inotropic therapy for hemodynamic maintenance, and underwent CRT implantation while on inotropic support.

2.3. Echocardiographic evaluation

All patients underwent routine echocardiography before and after CRT device implantation. Standard 2-dimensional echocardiography and Doppler imaging were performed by well-trained echocardiographists and reviewed by cardiologists. LV end-diastolic diameter (LVDD), LV end-systolic diameter (LVDS), and LVEF were measured using the modified biplane Simpson rule [10]. For quantification of mitral regurgitation (MR), apical 4-chamber images were used. MR was characterized as none=0, mild=1 (jet area/left atrium [LA] area $<10\%$), moderate=2 (jet area/LA area 10–20%), moderate-severe=3 (jet area/LA area 20–45%), and severe=4 (jet area/LA area $>45\%$).

2.4. Device implantation and management

All patients underwent CRT implantation under general anesthesia and mechanical ventilation. All pacing and defibrillator systems were implanted transvenously. During the procedure, the sensing and pacing thresholds were measured.

During follow-up, device interrogation was scheduled, and the pacing/sensing thresholds and arrhythmic events were checked. CRT optimization, including adjustment for atrioventricular and interventricular timing, was performed using echocardiography at 1 month and when necessary after device implantation.

2.5. Clinical response and endpoints

The clinical response to CRT was evaluated at 3 months follow-up. All adverse cardiac events, including all hospitalizations due to a cardiac cause, all deaths, and all lethal arrhythmic events were followed. In addition, the number of survival discharge or in-hospital deaths after CRT was also identified. LVAD implantation was considered as the endpoint in this study.

2.6. Statistical analysis

A p-value of <0.05 was considered statistically significant. Continuous variables are expressed as mean $\pm$ SD. For pairwise comparisons, a paired t test was used for normally distributed data. Non-normally distributed data were compared using the Wilcoxon signed rank test. All tests were 2-sided. The survival function was computed as the time of implantation to the event. The observation was censored at the time of the last known follow-up or at the time of the events. Event-free survival curves were calculated according to the Kaplan–Meier method. Statistical analysis was performed using the JMP 10 software.

3. Results

3.1. Baseline characteristics

We retrospectively reviewed 26 consecutive inotrope-dependent class IV patients who underwent CRT at our institution. The baseline characteristics of the eligible patients are shown in Table 1. All patients had a depressed LVEF ($23 \pm 7\%$), wide QRS complex (159 ± 38 ms), and high brain natriuretic peptide (BNP) level (608 ± 481 pg/mL). Concerning the etiology of the underlying heart disease, ischemic heart disease occurred in 15% and non-ischemic heart disease occurred in 85%.

3.2. Inotropic support and mechanical support

Intravenous inotropic therapy was administered for 72 ± 56 days before CRT implantation and consisted of dobutamine ($n=24$; 3.0 ± 1.2 μg kg^{-1} min^{-1}), dopamine ($n=2$; 4.5 ± 2.1 μg kg^{-1} min^{-1}), and/or milrinone ($n=13$; 0.12 ± 0.09 μg kg^{-1} min^{-1}). Three patients

Table 1
Baseline characteristics of the inotrope-dependent class IV patients.

Clinical parameters	Inotrope-dependent class IV patients ($n=26$)
Age (years)	55 ± 18
Male (%)	19 (73%)
Ischemic etiology (%)	4 (15%)
Diabetes (%)	6 (23%)
Chronic kidney disease (%)	12 (48%)
CRT-D/CRT-P (%)	20 (77%)/6 (23%)
SR (%)	16 (62%)
Permanent AF (%)	10 (38%)
QRS duration (ms)	159 ± 38
History of sustained VT (%)	8 (31%)
History of VF (%)	2 (8%)
Echocardiographic parameters	
LVEF (%)	24 ± 7
LVDD (mm)	71 ± 9
LVDS (mm)	62 ± 10
Mitral regurgitation (grade)	2.3 ± 0.9
Conduction disorders (%)	
Left bundle-branch block	11 (42%)
Intraventricular conduction delay	10 (38%)
Right bundle-branch block	5 (19%)
Medications (%)	19 (73%)
ACE inhibitor or ARB	23 (88%)
β-Blocker	17 (65%)
Amiodarone	26 (100%)
Diuretics	11 (43%)
Digoxin	

CRT-D: cardiac resynchronization therapy with defibrillator; CRT-P: cardiac resynchronization therapy pacemaker; SR: sinus rhythm; AF: atrial fibrillation; VT: ventricular tachycardia; VF: ventricular fibrillation; LVEF: left ventricular ejection fraction; LVDD: left ventricular end-diastolic diameter; LVDS: left ventricular end-systolic diameter; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers.

required mechanical ventilatory support. After CRT implantation, the intravenous inotropic agents were gradually decreased, and 20 of 26 patients (77%) were able to withdraw from inotropic support. The average time to weaning from inotropic therapy was 70 ± 70 days.

3.3. Follow-up clinical evaluation

At 3 months follow-up, the symptoms of HF improved in 20 (77%) patients to NYHA class I ($n=1$), class II ($n=10$), class III ($n=4$), and class IV without inotropic support ($n=5$). However, after CRT implantation, 3 (12%) patients died within 3 months and 3 (12%) patients could not withdraw from inotropic support (Fig. 1). Concerning echocardiographic changes after 3 months follow-up, the LV systolic function and LV volumes showed no significant changes after CRT implantation (LVEF at baseline: 23 ± 7% vs. at 3 months follow-up: 25 ± 9%; $p=0.23$, LVDD at baseline: 70 ± 9 mm vs. at 3 months follow-up: 68 ± 9 mm; $p=0.14$, LVDS at baseline: 61 ± 10 mm vs. at 3 months follow-up: 60 ± 9 mm; $p=0.18$); however, the MR significantly decreased (mean grade at baseline: 2.2 ± 1.0 vs. at 3 months follow-up: 1.7 ± 1.0, $p<0.005$). Other changes in clinical parameters from pre-CRT to post-CRT are listed in Table 2. The BNP levels decreased significantly after CRT implantation compared with those before CRT implantation (pre-CRT: 608 ± 481 pg/mL vs. post-CRT: 452 ± 391 pg/mL, $p=0.021$).

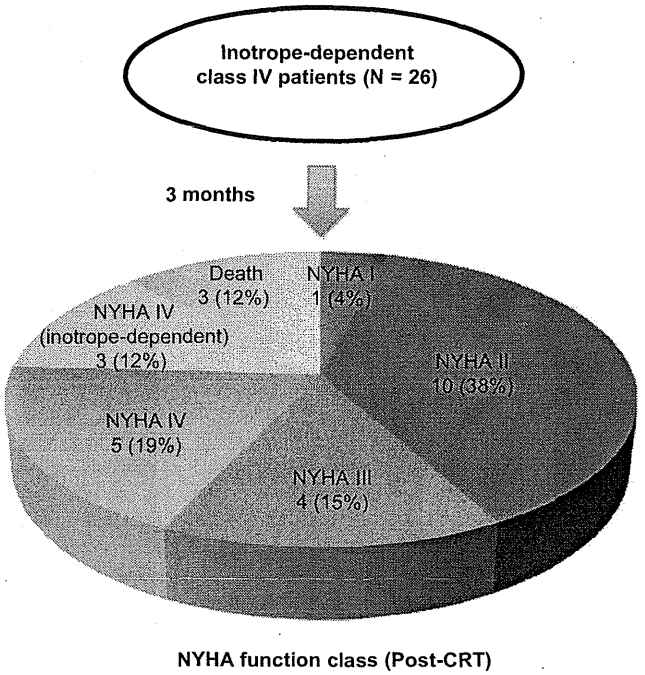

Fig. 1. Changes of New York Heart Association (NYHA) functional class at 3 months follow-up. The symptom of heart failure improved in 20 (77%) patients to NYHA class I ($n=1$), class II ($n=10$), class III ($n=4$), and class IV without inotropic support ($n=5$). However, 3 (12%) patients died within 3 months and 3 (12%) patients could not withdraw from inotropic support.

Table 2
Changes after CRT in inotrope-dependent class IV patients.

Variables	Pre-CRT	Post-CRT	*p* Value
LVEF (%)	23 ± 7	25 ± 9	0.23
LVDD (mm)	70 ± 9	68 ± 9	0.14
LVDS (mm)	61 ± 10	60 ± 9	0.18
Mitral regurgitation	2.2 ± 1.0	1.7 ± 1.0	0.008
BNP (pg/mL)	608 ± 481	452 ± 391	0.021
Hemoglobin (g/dL)	11.4 ± 1.8	11.6 ± 1.8	0.92
Sodium (mEq/L)	134.3 ± 4.1	135.8 ± 4.7	0.043
Creatinine (mg/dL)	1.25 ± 0.58	1.16 ± 0.44	0.84
Total bilirubin (mg/dL)	1.02 ± 0.67	0.68 ± 0.47	< 0.001

CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction; LVDD: left ventricular end-diastolic diameter; LVDS: left ventricular end-systolic diameter; BNP: brain natriuretic peptide.

3.4. Clinical outcomes

During a mean follow-up of 1033 ± 742 days, 9 (35%) patients died within 2 years and 13 (50%) patients experienced 1 or more episodes of ventricular tachyarrhythmia or sudden cardiac death after CRT. Among those patients, 20 (77%) survived to hospital discharge, and the 1-year survival rate was 81%. However, 68% of the study patients had an episode of HF rehospitalization during the follow-up period. Only 1 patient had successful cardiac transplantation, and 6 patients required LVAD implantation. Fig. 2 shows the event-free survival curve for all-cause death or LVAD implantation. The 1-year and 2-year survival rates were 81% and 65%, respectively. Fig. 3 shows the event-free survival curve for HF rehospitalization among the patients who survived to hospital discharge after the successful withdrawal of inotropic support. The 1-year and 2-year event-free survival rates were 65% and 44%, respectively. Fig. 4 shows the event-free survival curve for ventricular tachyarrhythmias or sudden cardiac death after CRT. On the basis of the analysis, lethal ventricular arrhythmias occurred frequently within 100 days. The event-free rate at 1-year was 65%.

4. Discussion

Our study had 3 major findings. First, most of the inotrope-dependent patients can withdraw from inotrope therapy and be discharged from the hospital after CRT implantation. Second, concerning echocardiographic parameters, CRT did not result in significant LV reverse remodeling among our study patients at 3 months follow-up. Finally, CRT improved the symptoms and short-term outcome in patients with inotrope-dependent class IV end-stage HF.

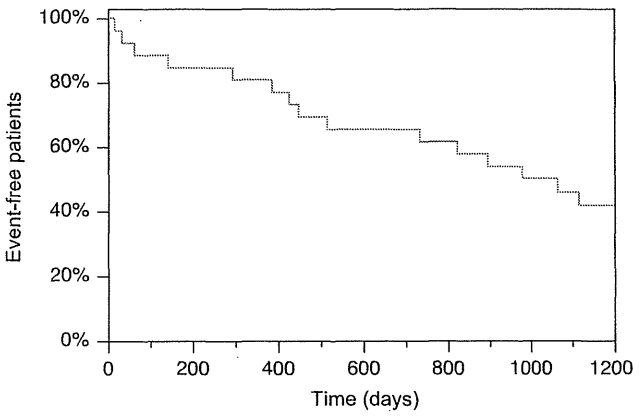

Fig. 2. Cumulative probability of survival for patients with inotrope-dependent class IV heart failure after cardiac resynchronization therapy (CRT) implantation. The Kaplan–Meier curve for all-cause mortality in patients with inotrope-dependent class IV heart failure after device implantation indicates that the 1-year and 2-year survival rates were 81% and 65%, respectively.

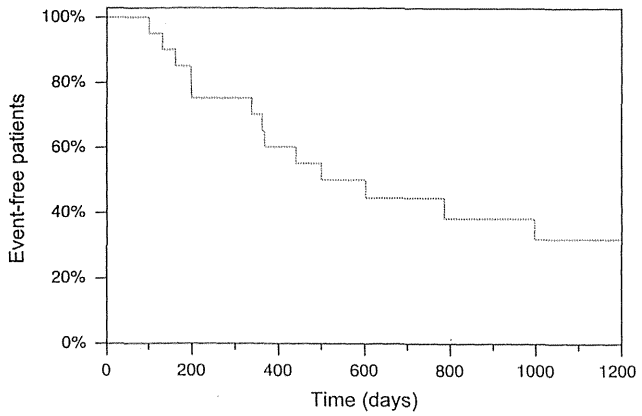

Fig. 3. Cumulative free probability of heart failure (HF) hospitalization in patients with inotrope-dependent class IV HF after cardiac resynchronization therapy (CRT) implantation. The Kaplan–Meier curve for HF hospitalization in patients with inotrope-dependent class IV HF who were discharged after device implantation shows that the 1-year and 2-year event-free survival rates were 65% and 44%, respectively.

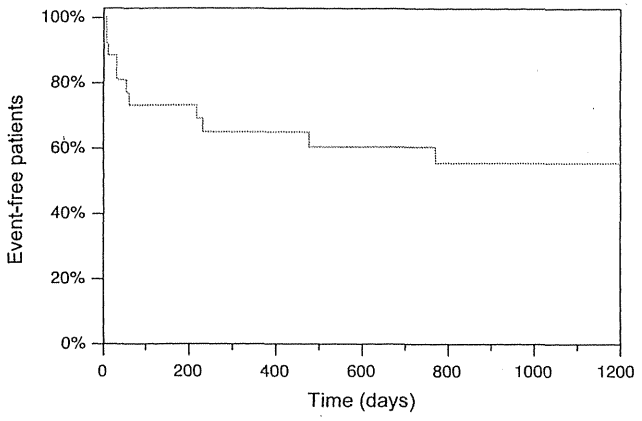

Fig. 4. Cumulative free probability of ventricular tachyarrhythmias or sudden cardiac death in patients with inotrope-dependent class IV heart failure (HF) after cardiac resynchronization therapy (CRT) implantation. The Kaplan–Meier curve for ventricular tachyarrhythmias or sudden cardiac death in patients with inotrope-dependent class IV HF after device implantation shows that lethal ventricular arrhythmia occurred frequently within 100 days, and the event-free rate at 1 year was 65%.

There are several reports about the clinical outcomes of patients with end-stage HF. The REMATCH trial reported extremely poor outcomes in the medical therapy—only group in patients with end-stage HF [1]. In that study, the optimal medical therapy group included 75% inotrope-dependent HF patients and the 1-year survival rate was only 25%. In relation to the comparison with LVAD patients, the HeartMate II trial studied the outcomes in continuous-flow LVAD patients [11]. Even in those patients, the 1- and 2-year survival rates were 68% and 58%, respectively. Our patients had similar baseline characteristics except that most had non-ischemic HF. However, the 1-year survival rate in our study population after CRT was 81%, which supports the favorable effects of CRT in patients with inotrope-dependent HF.

Herweg et al. [9] evaluated the benefit of CRT in 10 consecutive patients with NYHA class IV HF who were dependent on inotropic support. Their patients had received inotropic support for 146 ± 258 days, and all patients were alive at the mean follow-up of 1088 ± 284 days after CRT. They also reported an improvement in LVEF ($23.5 \pm 4.3\%$ to $32.0 \pm 9.1\%$; $p < 0.05$). Cowburn et al. [12] identified 10 patients who required inotropic support and underwent CRT while being administered with inotropic agents. All patients were weaned from inotropic agents and survived to hospital discharge. These reports are congruent with our report and support the beneficial effects of CRT for patients with inotrope-dependent HF. However, Adelstein et al. [13] reported conflicting findings. They divided their cohort of CRT patients into 3 groups according to exposure to intravenous inotropes before CRT—(1) no inotropes, (2) previous inotrope administration, and (3) dependent on inotropes—and compared the clinical outcomes. In their study, 16 inotrope-dependent patients were identified and the 1-year survival rate was $< 20\%$. In addition, inotrope-dependent patients exhibited neither functional improvement nor reverse remodeling in their study. The discrepancy between our study and their report may be partly explained by the fact that many of their patients had LVAD implantation and cardiac transplantation. It may be easier to assess LVAD or cardiac transplantation owing to the differences in social background. Moreover, most of our patients had non-ischemic cardiomyopathy, and were generally thought to benefit more from CRT than ischemic cardiomyopathy patients.

Bhattacharya et al. [14] also reported negative effects of CRT for patients with HF on inotropes at implantation. They retrospectively analyzed > 700 CRT-defibrillator recipients and categorized them as never on inotropes (NI group), weaned from inotropes before implantation, or on inotropes at implantation (II group). Their control group comprised patients with a standard defibrillator. They compared the overall survival and survival free from heart transplant or LVAD between those 4 groups. On the basis of their report, the II group patients demonstrated significantly shorter survival than the NI group patients at 12 months (hazard ratio, 2.95; 95% confidence interval, 1.05–8.35), and CRT may not have a survival advantage over a standard defibrillator for patients who had received inotropes before CRT. The propensity score-adjusted event-free survival rate in II group patients with regard to LVAD and heart transplantation at 12 months was around 60%, and the overall survival at 12 months was about 70%. Their survival rate was much better compared with that in the previously described reports; however, the authors reported no beneficial effects of CRT for inotrope-dependent HF patients. Their cohort was the largest study cohort of CRT patients on inotropic support; however, the II group was not exactly inotrope-dependent (i.e., they simply defined the II group as patients on inotropes at CRT implantation). Furthermore, the control group of patients with a standard defibrillator comprised only 3% of NYHA class IV patients, and these control group patients were thought to have milder HF than the II group patients. From this point of view, the effectiveness of CRT in inotrope-dependent HF patients could not be entirely denied.

4.1. Clinical implications

Previous large CRT trials excluded patients with NYHA class IV HF on inotropic support. Thus, the clinical evidence associated with the role of CRT in the management of those patients was unclear. On the basis of the results of our study, $> 75\%$ of the studied patients showed improvement in HF symptoms, and the 1-year survival rate was $> 80\%$. The findings of this study strongly support the beneficial effects of CRT even in inotrope-dependent HF patients.

We have shown the event-free survival curve for ventricular tachyarrhythmias after CRT implantation in this study. The incidence of lethal ventricular arrhythmias was remarkably high especially within 100 days after CRT implantation. This finding may be related to the unstable hemodynamics owing to weaning from inotropes or the proarrhythmic effects of biventricular pacing [15–17]. These observations raise the concern that patients with

inotrope-dependent HF would need to be managed carefully in the early phase after CRT to avoid arrhythmic events.

Concerning the mechanical changes after CRT, the eligible patients did not show significantly increasing LVEF and decreasing LV volume despite the improving MR at 3 months follow-up. The discrepancy between prognostic and mechanical improvement after CRT is probably attributable to the inotropic therapy itself. Inotropic agents usually emphasize systolic function and the pre-CRT LVEF could be overestimated. The changes in BNP level, serum sodium, and total bilirubin in patients after CRT implantation support the improvement in their hemodynamics. Even if significant reverse remodeling was not observed after CRT in this study, the benefit of CRT for functional improvement could not be denied. The prognosis of patients with inotrope-dependent class IV end-stage HF is still very poor; however, in the absence of an indication for heart transplantation or LVAD as a destination therapy, CRT is one of the most important therapeutic options for those patients.

4.2. Study limitations

This study was a single-group, non-randomized, retrospective review study. Although this study had the largest population among studies on the effects of CRT in patients with inotrope-dependent class IV end-stage HF, the number of patients was still small. Further study with a large sample is needed to confirm the efficacy of CRT for patients with inotrope-dependent class IV end-stage HF. In addition, the influence of underlying comorbidities could be an important factor for determining prognosis besides CRT effects alone.

5. Conclusions

CRT did not result in significant reverse remodeling in patients with inotrope-dependent class IV end-stage HF. However, it contributed to dramatically improve the symptoms, hemodynamics, and cardiovascular outcomes at least in a short-term period in some patients.

Conflict of interest

There was no financial support from any specific company for this study or any conflict of interest, and no specific unapproved use of any compound or product was made.

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