Change in Blood Pressure Just After Initiation of Cardiac Resynchronization Therapy Predicts Long-Term Clinical Outcome in Patients With Advanced Heart Failure

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Background The aim of this study was to retrospectively investigate the long-term effect of cardiac resynchronization therapy (CRT) and to clarify the useful predictors of clinical outcome.

Methods and Results The study group comprised 43 patients with advanced heart failure who underwent CRT (10 females; 66 ± 10 years): 23 were in sinus rhythm (SR group) and 20 had chronic atrial fibrillation (AF group). The clinical parameters and echocardiographic data were evaluated before and after CRT. There were no significant differences in the clinical parameters, echocardiographic data at baseline or frequency of responders between the 2 groups. In both groups, the clinical characteristics at baseline did not differ between the responders and non-responders. A prompt rise in systolic blood pressure (SBP) just after CRT was observed more often in responders than in non-responders, and SBP rise ≥ 5 mmHg was the only significant independent predictor of a CRT responder ($P=0.0033$). Furthermore, there was a significant difference in the event-free survival between patients with and without SBP rise ≥ 5 mmHg, demonstrated by Kaplan-Meier method, at 2 years of follow-up ($P=0.045$).

Conclusion A prompt BP rise just after CRT may predict short- and long-term clinical improvement in CRT recipients. (Circ J 2009; 73: 288–294)

Key Words: Blood pressure; Cardiac resynchronization therapy; Heart failure

Cardiac resynchronization therapy (CRT) improves the quality of life, symptoms, and exercise capacity of patients with drug-refractory congestive heart failure (HF) and intraventricular conduction delays¹. In addition, CRT has resulted in a reduction in HF hospitalizations and the risk of death^{1,2}. However, the indication for CRT remains limited by a fairly high percentage of non-responsive patients^{1,3}. Previous reports have suggested that baseline mechanical ventricular dyssynchrony may predict the hemodynamic response to CRT^{4,5} but there are some non-responders to CRT despite an improvement in the left ventricular (LV) dyssynchrony. Thus, predictors of CRT response and the long-term outcome of CRT have not been sufficiently clarified.

Atrial fibrillation (AF) often occurs in patients with advanced HF and in CRT recipients^{6,7} but previous large trials have examined the effectiveness of CRT only in patients with sinus rhythm (SR)^{1–4}. Therefore, the efficacy and safety of CRT for patients with AF have not been fully established.

The purpose of this study was to identify CRT responders

in order to predict the short- and long-term clinical outcomes and to examine the efficacy of CRT in patients with AF.

Methods

Study Population

This study included 43 patients (10 women; mean age, 66 ± 9 years) with advanced HF and a wide QRS complex who received a pacemaker or implantable cardioverter defibrillator providing biventricular pacing (Table 1). Fourteen (33%) patients had ischemic heart disease, 24 (56%) had idiopathic cardiomyopathy, 2 (5%) had valvular heart disease, 1 (2%) had arrhythmogenic right ventricular (RV) cardiomyopathy, and the remaining 2 (5%) had cardiac sarcoidosis. At the time of CRT, 18 (42%) patients were in New York Heart Association (NYHA) function class 4, and the remaining 25 (58%) were in class 3 despite maximal pharmacologic therapy before CRT. In all patients, the total QRS duration was >140 ms (range, 140–280 ms) and the LV ejection fraction (LVEF) determined by echocardiography was $<40\%$ (mean LVEF, $25 \pm 11\%$) with extensive dilation of the left ventricle (LV end-diastolic dimension, 70 ± 11 mm; Table 1). In total, 20 (47%) patients had chronic AF and the remaining 23 (53%) were in SR.

After assessing the patients' clinical status and examining their cardiac function by echocardiography before and 1 month after CRT initiation, they were divided into 2 groups: responders and non-responders. A responder was defined as a patient who improved clinically to NYHA function class I or II during the follow-up period and whose LV end-systolic volume (LVESV) decreased by 10% and/or LVEF

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Table 1 Clinical Characteristics and Measurement Variables

	All patients (n=43)	AF (n=20)	SR (n=23)	P value
Age (years)	66±9	69±9	64±10	0.1
Male gender (%)	33 (76%)	19 (95%)	14 (60%)	0.08
NYHA III/IV	25/18	14/6	11/12	0.2
Ischemic/non-ischemic	14/29	7/13	7/6	0.8
QRS duration (ms)	180±34	180±30	180±40	0.7
LV ejection fraction (%)	25±11	28±11	24±10	0.2
LV end-diastolic dimension (mm)	70±11	68±9	72±12	0.3
Left atrial diameter (mm)	51±9	55±10	48±7	<0.05
T-diff by TDI (ms)	64±37	79±44	57±34	0.2
Creatinine (mg/dl)	1.4±0.6	1.6±0.5	1.4±0.6	0.3
BNP (pg/ml)	755±541	726±528	795±570	0.7
Upgrade from a pacemaker (%)	11 (25%)	7 (35%)	4 (17%)	0.2
Responder (%)	17 (40%)	8 (40%)	9 (39%)	1.0

Values are mean±standard deviation.

A responder was defined as a patient who improved clinically to NYHA class I or II during the follow-up period and whose LV end-systolic volume decreased by 10% and/or LV ejection fraction increased by 10%.

AF, atrial fibrillation; SR, sinus rhythm; NYHA, New York Heart Association; LV, left ventricular; T-diff by TDI, difference in the time-to-peak velocity of the basal septum to the basal portion of the lateral wall of the left ventricle measured by tissue Doppler imaging; BNP, B-type natriuretic peptide.

Table 2 Characteristics of Cardiac Resynchronization Therapy Recipients (Responders vs Non-Responders)

	Responders (n=17)	Non-responders (n=26)	P value
Age (years)	68±10	69±8	0.7
Male gender (%)	13 (76%)	20 (77%)	1.0
NYHA III/IV	11/6	17/9	1.0
Ischemic/non-ischemic	6/11	8/18	0.8
QRS duration (ms)	190±30	170±34	0.2
LV ejection fraction (%)	23±13	27±9	0.3
LV end-diastolic dimension (mm)	67±11	71±11	0.2
Left atrial diameter (mm)	50±8	52±10	0.4
T-diff by TDI (ms)	74±38	57±35	0.1
Hemoglobin (g/dl)	12.9±1.8	13.0±1.5	0.8
Blood glucose level (mg/dl)	135±73	123±47	0.5
Creatinine (mg/dl)	1.4±0.6	1.4±0.5	1.0
BNP (pg/ml)	963±572	627±489	<0.05
Upgrade from a pacemaker (%)	6 (35%)	5 (19%)	0.2
Diuretic use (%)	17 (100%)	26 (100%)	1.0
ACEI or ARB use (%)	13 (76%)	21 (81%)	0.9
β-blocker use (%)	10 (59%)	17 (65%)	0.7
Pulse rate (beats/min)	68.9±10.0	71.3±7.5	0.38
ΔPulse pressure just after CRT (mmHg)	6.3±6.9	-1.2±7.0	0.0014
ΔSystolic BP just after CRT (mmHg)	9.0±8.0	-0.6±8.4	<0.001
Systolic BP just before CRT	109±23	103±17	0.3
Systolic BP just after CRT	119±22	102±19	<0.05

Values are mean±standard deviation.

ACEI, angiotensin converting enzyme; ARB, angiotensin receptor blockers; BP, blood pressure; CRT, cardiac resynchronization therapy. Other abbreviations see in Table 1.

increased by 10%. The clinical status was determined by 2 cardiologists who did not have any information concerning the CRT status of the patient.

Echocardiographic Examination and Tissue Doppler Imaging (TDI)

Transthoracic echocardiography, including TDI, was performed using a Vivid 7 cardiac ultrasound machine (General Electric, Vingmed Ultrasound, Horten, Norway) as previously described^{8,9} The LV dimensions were measured by M-mode echocardiography in the parasternal long-axis view⁸ LV dyssynchrony (T-Diff) was determined as the difference in the time-to-peak velocity of the basal

septum to the basal portion of the lateral wall of the LV, and was determined during the ejection period of the cardiac cycle⁸

Device Implantation

At the time of device implantation, 23 (53%) patients were in SR and 20 (47%) presented with chronic AF with bradycardia. Eleven patients (26%) had already received a RV pacing system and they underwent an upgrade of the pacing system to allow for CRT. In patients who were in SR, a lead placed in the right atrial appendage. The LV pacing lead was advanced transvenously through the coronary sinus, and placed in the left marginal or posterolateral

Fig 1. Frequency of a prompt rise in the systolic blood pressure ≥ 5 mmHg just after initiating cardiac resynchronization therapy and of a prompt rise in the aortic pulse pressure ≥ 5 mmHg. The frequency of a prompt rise in systolic blood pressure was significantly greater in the responders than in the non-responders. AF, atrial fibrillation; SR, sinus rhythm.

Fig 2. Prompt rise in systolic blood pressure (SBP) in a 77-year-old man with ischemic cardiomyopathy. Just after initiating cardiac resynchronization therapy (CRT), SBP rose from 120 mmHg to 129 mmHg and after 1 month, his New York Heart Association class had improved from III to I and his left ventricular ejection fraction from 29% to 40%. BP, blood pressure.

cardiac vein in 38 patients. The remaining 5 patients underwent an intraoperative CRT system implantation, using epicardial pacing wires placed on the anterolateral wall of the LV. The RV lead was placed at the apex in all patients.⁸ The atrioventricular (AV) interval was optimized for maximal diastolic filling as determined by Doppler echocardiography.¹⁰ However, because the available devices only allowed for simultaneous stimulation of the RV and LV in most patients, there was no optimization of the interventricular delay (V-V delay), and therefore both ventricles were paced simultaneously in all patients. After device implantation, the patients underwent follow-up (1 week after implantation, then every 1–3 months in the cardiology clinic).

During device implantation, blood pressure (BP) was continuously monitored using an arterial line via a 4Fr sheath in the right femoral artery. The BP changes were measured when biventricular pacing started just after AAI

pacing in the patients with SR, and just after VVI pacing in the patients with AF. The BP and pulse rate were also measured in the morning of the day of device implantation and in the morning 1 week after implantation.

Statistical Analysis

Continuous variables are expressed as the mean $\pm$ standard deviation. Student's t-test was used to compare groups. Analysis of variance (ANOVA) was used when comparisons involved more than 2 groups. When group differences were found, a 1-way ANOVA was followed by the Fisher's protected least significant difference method to test the significance of the difference among the means in all groups. The long-term response was measured as the combined endpoint of hospitalization for HF and/or all cause mortality at 24 months. The time to the primary endpoint was estimated by the Kaplan-Meier method, with comparisons

Table 3 Settings of the CRT and Clinical Parameters (Responders vs Non-Responders)

	Responders (n=17)	Non-responders (n=26)	P value
Pacing mode (DDD/VVI)	9/8	13/13	0.9
AV delay (ms)	125±27	122±35	0.9
ΔPulse rate (beats/min)	+5.5±5.5	+4.4±7.0	0.6
Pulse rate before CRT	68.9±10.0	71.3±7.5	0.4
Pulse rate 1 week after CRT	74.5±7.0	75.6±9.1	0.7
ΔSystolic BP 1 week after CRT (mmHg)	+2.06±10.6	+0.27±9.2	0.6
Systolic BP before CRT	96.8±10.6	98.1±13.3	0.7
Systolic BP 1 week after CRT	98.9±10.6	98.4±12.4	0.9
ΔDiastolic BP 1 week after CRT (mmHg)	+2.71±9.3	+0.62±6.1	0.4
Diastolic BP before CRT	62.4±11.6	59.6±10.8	0.4
Diastolic BP 1 week after CRT	65.1±9.8	60.2±11.8	0.2

Values are mean±standard deviation.

Systolic and diastolic BPs and pulse rate were measured in the morning of the day of device implantation and in the morning 1 week after implantation.

Abbreviations see in Tables 1,2.

Table 4 Ventricular Dyssynchrony Before and After CRT in Patients With AF or SR

	Responder	Non-responder	P value
AF group	n=8	n=12	
Before CRT (ms)	79±44	69±39	0.6
1 month after CRT (ms)	30±28	54±32	0.1
P value (before vs after CRT)	<0.01	0.2	
SR group	n=9	n=14	
Before CRT (ms)	71±36	48±31	0.1
1 month after CRT (ms)	22±25	28±21	0.5
P value (before vs after CRT)	<0.05	0.1	

Values are mean±standard deviation.

Abbreviations see in Tables 1,2.

made using the log-rank test with Statview software (SAS institute, Cary, NC, USA). Categorical variables were compared using chi-squared analysis with the Yate's correction if necessary. An overall chi-square test for a 2×n table was performed when comparisons involved more than 2 groups. Multivariate analysis with logistic regression was performed to isolate the independent criteria of responders before CRT. Only the variables that were significant at a 0.2 level in the univariate analysis were included in the multivariable logistic regression. A P-value <0.05 was considered significant.

Results

CRT Responders vs Non-Responders

Based on their clinical status and cardiac function before and 1 month after CRT, 17 patients (40%) were classified as responders and 26 (60%) were non-responders (**Table 2**). There was no significant difference in the clinical status, NYHA functional class, QRS duration, echocardiographic parameters, T-Diff, serum creatinine or prevalence of an upgrade from a pacemaker to a CRT device between the responders and non-responders (**Table 2**). However, the plasma B-type natriuretic peptide (BNP) concentration (P<0.05) was higher and the change in the systolic BP (SBP; P<0.001) and in the aortic pulse pressure (P=0.0014) just after the initiation of CRT was greater in the responders than in the non-responders (**Table 2**). A prompt SBP rise ≥5 mmHg was found in 14 (82%) of the responders, the frequency of which was greater than that in the non-responders (27%; P<0.0005; **Figs 1,2**). No significant difference was

found between the responders and non-responders in the changes in pulse rate before and 1 week after CRT, pacing mode or setting of the AV delay (**Table 3**). Further, the systolic and diastolic BP before (on the morning of device implantation) or 1 week after CRT, and their change did not differ between the responders and non-responders (**Table 3**).

SR vs AF

In patients with AF, the left atrial diameter was larger than in those with SR (P<0.05; **Table 1**). However, no significant difference was found in the clinical status, NYHA functional class, QRS duration, echocardiographic parameters, T-Diff, serum creatinine and plasma BNP concentrations or the prevalence of an upgrade from a pacemaker to a CRT device between the patients with AF and those in SR (**Table 1**). The incidence of responders did not differ between the 2 groups either. In the patients with either AF or SR, the incidence of a prompt SBP rise ≥5 mmHg was greater in the responders than in the non-responders (**Fig 1**).

Before CRT, the T-Diff did not significantly differ between the responders and non-responders among patients with AF or in those in SR (**Table 4**), although those values were greater in the responders than in the non-responders. At 1 month after CRT, it had improved significantly in the responders, but not in the non-responders among patients with AF or SR.

Predictors of a Responder at 1 Month After CRT

The univariate logistic regression analysis including age, gender, presence of coronary disease, HYHA class, plasma

Table 5 Multivariate Statistical Analysis With Logistic Regression: Independent Predictive Factors for Identifying Responders to CRT

	Responders (n=17)	Non-responders (n=26)	OR (95%CI)	P value
Systolic BP rising after CRT (≥ 5 mmHg)	82%	27%	12.1 (2.3–64.5)	0.0033
BNP (>600 pg/ml)	68%	38%	5.2 (0.99–27.0)	0.051

OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

Fig3. Kaplan-Meier curves showing the event-free survival after cardiac resynchronization therapy over 24 months for the patients with and without a rise in systolic blood pressure (BP) ≥ 5 mmHg. Events are defined as death or hospitalization caused by heart failure. There was a significant difference in the long-term outcome at 2 years of follow-up between the 2 groups.

BNP and serum creatinine concentrations, QRS duration, LVEF, T-Diff and systolic BP rise just after CRT showed that a prompt SBP rise ≥ 5 mmHg ($P=0.0015$) and plasma BNP level ≥ 600 pg/ml ($P=0.036$) were significantly associated with responders to CRT. The multivariable logistic regression showed that a prompt SBP rise ≥ 5 mmHg was the only independent predictor of a responder to CRT (**Table 5**).

Predictor of Long-Term Clinical Improvement in CRT Recipients

To clarify the parameters for predicting the long-term outcome after CRT, Kaplan-Meier survival analysis was performed as a combined endpoint of hospitalization for HF and/or all-cause mortality at 24 months (**Fig3**). A trend toward improved survival among the patients with a prompt SBP rise after CRT was observed; the difference in the survival of patients with a prompt SBP rise ≥ 5 mmHg vs patients without a SBP rise was statistically significant ($P=0.045$, log-rank test).

Discussion

Major Findings

The results of this study demonstrate that a prompt SBP rise is a useful parameter for predicting long-term clinical improvement in CRT recipients, as well as CRT responders shortly after CRT, irrespective of prior AF or SR, and that patients with AF can obtain comparable benefits from CRT to those in SR.

CRT Predictors and SBP Rise

Several studies have attempted to identify the predictors of a response to CRT using either patient selection criteria, such as the QRS width,^{11,12} BNP concentration,¹³ measurements of baseline asynchrony using echocardiography,^{4,14} myocardial dyssynchrony assessed by the cardiovascular magnetic resonance-tissue synchronization index,¹⁵ or pacing site selection.¹⁶ Most of those studies have been limited by the fact that there was usually more than 1 predictive factor in determining the response within the individual patients. Based on the results of those studies,^{5,11} ventricular dyssynchrony has become a major determinant for predicting CRT effectiveness, but because there are some non-responders to CRT despite an improvement in the ventricular dyssynchrony,^{4,5,8,11,14} it may not be the only useful parameter for predicting the outcome after CRT. It has become clear that the distance and position of the pacing leads and viability of the LV lateral wall may affect the CRT response.¹⁶ Furthermore, few studies have examined the utility of those predictors regarding long-term clinical outcome,^{4,11,14,16} so predictors of both short- and long-term outcome after CRT have not been fully clarified.

An acute improvement in cardiac output or stroke volume has been reported as a good predictor, and was assessed in most studies by the change in aortic pulse pressure.^{17–20} It is well known that aortic pulse pressure directly correlates with cardiac output at a constant heart rate and vascular load,²¹ so most studies have examined pulse pressure as a measurement variable. However, a significant correlation between the changes in pulse pressure and clinical outcome was not found in those studies^{17–20} and none have reported that a rise in SBP predicts the short- and long-term clinical outcome after CRT.

It is well known that BP and pulse pressure are easily influenced by numerous factors, including autonomic nerve activity, fluid and electrolyte balance, and status of the renin-angiotensin system, which may be why in the present study no significant correlation was found between BP or pulse pressure 1 week after CRT or between the changes in BP or pulse pressure 1 week after CRT and the clinical outcome. On the contrary, we found that a prompt rise in the pulse pressure was found more often in responders than in the non-responders, and that a prompt rise in SBP predicted not only the short-term benefits but also long-term survival over 24 months of follow-up. These findings suggest that the prompt rise in SBP is a good predictor of clinical outcome and we consider that continuous monitoring and measurement of the BP just before and after CRT in this study avoided inclusion of the all the factors affecting BP other than CRT initiation. Therefore, we believe that a prompt rise in SBP, even if its magnitude is small, can predict the clinical outcome after CRT.

Proposed Mechanism of the SBP Rise After CRT

In the present study, a prompt rise in SBP predicted the

short- and long-term outcomes of CRT. Generally, the major mechanisms of an increase in BP are an improvement in the EF, cardiac output and other parameters of cardiac function, and a reduction in mitral regurgitation as a result of an improved intraventricular synchrony. It is well known that these favorable results of CRT depend on the level of baseline intraventricular dyssynchrony, lead position, AV delay setting and myocardial viability at the lead positions. Because the AV delay setting and the position of the LV leads were almost always appropriate, and the baseline intraventricular dyssynchrony did not differ between the responders and non-responders in our population, we suggest that myocardial viability was related to the BP rise after CRT. However, it is difficult to determine the effective mechanism most responsible for the results, because improved chamber loading, reduced mitral regurgitation, and enhanced contractile function each could explain the observation. Therefore, we suggest that BP changes can simply indicate the clinical outcome because they are the result of the multiple hemodynamic effects of CRT.

For this study, we restricted our analysis to endpoints such as mortality and hospitalization for HF. Medical therapy after CRT was left to the physician's discretion, making it possible that changes in drug therapy could have influenced the clinical outcome. Because the patients with a rise in SBP were able to receive an adequate amount of drugs (β -blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and diuretic agents), it is possible that the clinical outcome was improved medically in those patients. However in our population, none of the patients received drugs that would cause a BP rise.

Comparison of Response to CRT in Patients With SR vs Chronic AF

Although some studies have shown an acute hemodynamic response in patients with chronic AF who have undergone CRT, there is limited evidence about the long-term effects of CRT in patients with chronic AF.^{19,22–24} Molhoek et al studied patients with and without chronic AF and showed that their clinical parameters improved after 6 months of CRT and the rate of non-responders was greater among patients with AF.²² Delnoy et al showed that the benefit of CRT in patients with chronic AF and HF was similar to that in patients with SR, and that long-term survival after CRT did not differ between the AF and SR groups.²⁵ We evaluated the clinical and echocardiographic effects of CRT in patients with and without chronic AF and there was no significant difference in the frequency of responders between the AF and SR groups, which was a similar finding to that of a previous report.²² In both groups, the LV dyssynchrony in the responders improved significantly compared with that in the non-responders. A prompt SBP rise ≥ 5 mmHg after CRT occurred more frequently in responders than in non-responders, which shows that it is a good predictor of the response to CRT in patients not only with SR, but also in those with chronic AF.

Clinical Implications

CRT is a recognized emerging treatment for patients with advanced HF, but the ideal candidates are still a matter of discussion. Although many possible predictors of the response to CRT have been reported, it is difficult to identify the patients in whom implantation of the device will improve the prognosis. In our study population, a prompt SBP rise just after initiating CRT was a simple parameter

to measure and a good predictor for responders to CRT; however, it is possible that the predictive value is not adequate for correctly identifying responders. Furthermore, it is necessary to perform invasive hemodynamic examinations using temporary leads in order to select candidates for CRT, so a SBP rise after CRT should be used as a positive predictor in combination with other predictors such as the QRS width or baseline asynchrony.

Study Limitations

First, because this study was not designed prospectively in order to analyze the clinical outcome after CRT and because the number of patients analyzed was small, future studies with a larger sample size and in a prospective fashion may be needed to clarify our results. Second, optimizing the V-V delay was not performed in this study and tailored and optimal programming of the V-V delay might affect the results after CRT. Third, we raised the possibility of myocardial viability as a factor affecting BP rise after CRT, but no examinations to determine myocardial viability, such as scintigraphy, were performed in this study.

Conclusions

The data from our study indicate that a prompt rise in SBP after initiating CRT is a good predictor of the clinical outcome. Further studies in large patient cohorts are needed to more clearly define the clinical characteristics of patients who exhibit such a rise in BP after initiating CRT.

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