Cardiac Resynchronization Therapy for Various Systemic Ventricular Morphologies in Patients With Congenital Heart Disease

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Background: Cardiac resynchronization therapy (CRT) can result in functional improvement and reduced mortality in patients with medically refractory heart failure. Although CRT is reportedly effective in patients with congenital heart disease (CHD), it is still controversial in patients who have systemic right ventricle.

Methods and Results: Twenty CHD patients treated with CRT since 2006 were divided into 3 groups based on systemic ventricular (sysV) morphology (7 with left ventricle [sLV], 7 with right ventricle [sRV], and 6 with unbalanced 2 ventricles as a single-ventricular physiology [sBV]). The acute effects of CRT on hemodynamics and sysV function before device implantation was retrospectively evaluated and the chronic (≥6 months) effects of CRT on late outcomes was assessed. In our CHD populations, sysV volume index was reduced from 139±41 to 118±33 ml/m² (P=0.04) after CRT, and there was significant improvement in B-type natriuretic peptide levels (from 341±384 to 160±152 pg/ml, P=0.01) and New York Heart Association (NYHA) functional class (from 2.1±0.6 to 1.8±0.7, P=0.02) on a late outcome. The sRV group did not show a late sysV volume reduction despite significant QRS shortening, and an increase of sysV peak dP/dt in the acute study differed from that of other groups.

Conclusions: CRT improves late hemodynamic and functional status in sLV and sBV CHD patients with a dys-synchronized sysV. However, an acute CRT effect cannot guarantee long-term benefit in sRV patients. (Circ J 2015; 79: 649–655)

Key Words: Cardiac resynchronization therapy; Congenital heart disease; Dyssynchrony; Reverse remodeling; Systemic right ventricle

Cardiac resynchronization therapy (CRT) has been shown to benefit patients with congestive heart failure.1–5 However, limited data are available on CRT in patients with congenital heart disease (CHD).6–10 Some studies on the use of CRT for CHD have shown that the efficacy of CRT pacing for patients with a systemic right ventricle (RV) or univentricular heart is not conclusive.

In an adult congestive heart failure series, ischemic heart disease has been found to be a significant predictor of the lack of a response to CRT.11 Furthermore, a higher overall scar burden, large number of severely scarred segments, and greater scar density near the left ventricle (LV) leads to an unfavorable response to CRT in ischemic cardiomyopathy patients. Myocardial fibrosis, as determined via late gadolinium enhancement (LGE) cardiovascular magnetic resonance imaging (cMRI), might occur in patients with a systemic RV.12 Moreover, the extent of the LGE correlates with the age, ventricular dysfunction, and electrophysiological parameters. These features are analogous to those of ischemic heart disease. Hence, the effectiveness of CRT for patients with CHD, especially a systemic RV, is not conclusive.

Study Design
The Ethics Committee of the National Cerebral and Cardiovascular Center approved our retrospective study. Our strategy for CRT implantations was based on an acute hemodynamic study, which we performed prior to the device implantation in order to evaluate the acute effect of the CRT and to determine the optimal pacing sites; that is, the acute hemodynamic study
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who could not undergo conventional bi-ventricular surgical correction, which included various complex morphologies (Table). The sLV patients had a morphological LV as a sysV, and in contrast, the sRV patients did not have a morphological LV or a pulmonary ventricle. The sBV patients had 2 unbalanced ventricles that were unsuitable for conventional bi-ventricular surgical repair on the grounds of various inadequacies such as unilateral ventricular hypoplasia and structural disturbances of the atrio-ventricular valve. We evaluated the acute effect of CRT on the hemodynamics and sysV function before the device implantation, and then assessed the chronic (≥6 months) impact of CRT, including the plasma B-type natriuretic peptide (BNP) level and New York Heart Association (NYHA) functional class.

**Acute Hemodynamic Study**

We performed an electrophysiology study before the introduction of CRT pacing to evaluate the efficacy of the CRT. We evaluated the hemodynamics and sysV function, such as the QRS duration, peak +dP/dt, ejection fraction (EF), end-diastolic pressure (EDP), and central venous pressure (CVP) that was followed by a device implantation, and 6 months after the implantation, the chronic effects of the CRT were evaluated. In this study, dyssynchrony was defined as the presence of electrical dyssynchrony that was confirmed by electrocardiograms with a QRS duration of greater than 130 ms. A retrospective review was performed of all available clinical data, electrocardiograms, cardiac catheterizations, and clinical outcomes in those patients who underwent a CRT at the National Cerebral and Cardiovascular Center between January 2006 and December 2012.

**Patients**

The study population consisted of 20 CHD patients (mean age, 22±13 years) who had been treated with CRT at our institution. We divided the patients into 3 groups based on the type of systemic ventricle (sysV), including 7 patients with a systemic LV (sLV), which included a double-inlet LV after a ventricular septation and tetralogy of Fallot; 7 with a systemic RV (sRV), which included a congenitally or surgically corrected transposition of the great arteries; and 6 with 2 unbalanced ventricles as an univentricular physiology (sBV) who could not undergo conventional bi-ventricular surgical correction, which included various complex morphologies (Table). The sLV patients had a morphological LV as a sysV, and in contrast, the sRV patients did not have a morphological LV or a pulmonary ventricle. The sBV patients had 2 unbalanced ventricles that were unsuitable for conventional bi-ventricular surgical repair on the grounds of various inadequacies such as unilateral ventricular hypoplasia and structural disturbances of the atrio-ventricular valve. We evaluated the acute effect of CRT on the hemodynamics and sysV function before the device implantation, and then assessed the chronic (≥6 months) impact of CRT, including the plasma B-type natriuretic peptide (BNP) level and New York Heart Association (NYHA) functional class.

### Table. Patient Characteristics

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<td>CRT-P</td>
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AF, atrial fibrillation; APC, atrio-pulmonary connection; AVSD, atrioventricular septal defect; BDG, bidirectional Glenn; BTS, Blalock-Taussig shunt; CAVC, common atrioventricular canal; cPS, critical pulmonary stenosis; CRT-D, cardiac resynchronization therapy (CRT) defibrillator; CRT-P, CRT pacemaker; cTGA, corrected transposition of the great arteries; DDD, conventional dual chamber pacemaker; DILV, double inlet left ventricle; DORV, double inlet right ventricle; ECG, extra-cardiac conduit; FR, functional repair; Liso, left atrial isomerism; LV, left ventricle; MAPCA, major aortopulmonary collateral arteries; NYHA, New York Heart Association; PA, pulmonary atresia; PAB, pulmonary arterial banding; PM, pacemaker; Riso, right atrial isomerism; RVOTR, right ventricular outflow tract reconstruction; sBV, unbalanced 2 ventricles as a single ventricular physiology; sLV, left ventricle systemic ventricle; s/p, status of post; sRV, right ventricle systemic ventricle; sysV-EF, systemic ventricle-ejection fraction; TCPC, total cavopulmonary connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TVR, tricuspid valve replacement; UF, unifocalization; VS, ventricular septation.
during dual-site pacing and intrinsic beats. At first, we roughly mapped the sysV to determine the electrical delay using a multi-polar catheter. Basically, among the sLV and sBV patients, we placed the pacing catheter at an opposite site to synchronize the sysV in the horizontal direction. In the sRV patients, we assumed the ideal pacing sites in the longitudinal direction. We paced the systemic RV between the RV inferior wall and outflow practically, if at all possible. The optimal pacing sites were determined in a comprehensive manner to consider the electrical conduction delay, ideal pacing direction, and shortening of the QRS duration. Basically, dual-site ventricular pacing was performed completely simultaneously. Furthermore, the atrio-ventricular pacing delay was adjusted before the acute study by echocardiography, as advocated by Ishikawa et al., in patients who were previously implanted with a permanent pacemaker, and determined at just the same timing as the intrinsic atrio-ventricular conduction. We used Simpson’s rule to estimate the right and left ventricular volumes and divided the end-diastolic ventricular volume by the body surface area to obtain the end-diastolic volume index (EDVI). We also calculated the sysV-EF. The sysV peak +dP/dt was measured using a Pressure Wire® Certus (St. Jude Medical, St. Paul, MN, USA). Optimal pacing sites were chosen from among several pacing sites based on the improvement in the sysV peak +dP/dt and shortening of the QRS duration. In the acute hemodynamic study, the heart rates under both conditions were carefully adjusted. Moreover, young children underwent the acute study under general anesthesia to help minimize the impact of anxiety or body movement, which could cause unstable hemodynamics.

Device Implantation
Conventional resynchronization therapy involves implantation of a transvenous pacing lead into the RV and a left ventricular lead placed transvenously into a coronary sinus branch. However, in our CHD series, this route was rarely feasible. Therefore, we had to implant the CRT system epicardially via a thoracotomy, depending on the ideal pacing sites that were chosen during the acute hemodynamic study. In patients for whom a transvenous lead implantation was not recommended (eg, small body size, single-ventricle physiology, corrected transposition of great arteries, or uncorrected cardiac defects), an epicardial lead placement was performed via a median sternotomy or lateral thoracotomy. In patients undergoing a transvenous lead placement, a left ventricular lead insertion was attempted using conventional techniques. In one case, 1 atrial and 2 ventricular leads were placed for a combined transvenous and epicardial approach.

Evaluation of the Chronic Effects of CRT
Approximately 6 months after the implantation of the CRT device, we recorded the BNP level and NYHA functional class in all patients. We also evaluated the sysV function, including the sysV-EDVI, sysV-EF, and QRS duration to determine the effect on the late outcomes. The sysV-EDVI and -EF were calculated by cine-angiograms based on a multiple-slice method. Biplane radiographic equipment, including cine-fluorographic units with filming speeds of 30 frames · s⁻¹, were used. To ensure valid measurements, ectopic or post-ectopic beats were avoided.

Electrocardiogram (ECG) Analysis
ECGs were reviewed to compare the QRS duration to age-based normal values. An analysis was performed on the ECG data obtained before the CRT implantation, during an acute hemodynamic study, and 6 months after the CRT. The QRS was measured in leads II, V1, and V5 for consistency, at a paper speed of 100 mm/s by a digital caliper using an EP-WorkMate® EP MedSystems Inc, West Berlin, NJ, USA) (EP MedSystems Inc, West Berlin, NJ, USA). All ECGs also underwent a secondary blinded review by a single investigator.

Statistical Analysis
Continuous data are expressed as the mean ± standard deviation. Comparisons between groups were made using a 2-tailed, unpaired Student’s t-test or Fisher’s exact test, as appropriate. A value of P<0.05 was considered statistically significant. The mean of the 3 groups were compared by a one-way ANOVA. For the post-hoc analysis, the Tukey HSD test was used to determine pairwise differences between groups, and the Dunnett’s test was used to determine significant differences between a given data set and the control values of the data set.

Results
Patient Characteristics
There were no significant differences between the groups in the baseline characteristics, which consisted of age, NYHA functional class, QRS duration before the CRT, and sysV-EF measured on cine-angiograms in the acute hemodynamic study. All patients also had electrical dyssynchrony (QRS duration ≥130 ms); of those, 11 had already undergone a pacemaker implantation and 2 patients in the sLV group were indicated for a pacemaker implantation because of advanced atrio-ventricular block. The other 6 patients were indicated for an upgrade of an advanced atrio-ventricular surgical correction. In the sRV group, 5 out of 7 cases had a congenitally or surgically corrected transposition of great arteries with a systemic RV.

All our patients were taking medications for heart failure at the time of the CRT initiation. The most common medications were diuretics and were used in 19 (95%) patients, followed by angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (18 patients; 90%), β-blockers (14 patients; 70%) and digoxin (10 patients; 50%).

Electrical Dyssynchrony
Twelve patients (60%) had electrical dyssynchrony during ventricular pacing, owing to having a permanent ventricular pacing system prior to the CRT initiation. We placed an additional ventricular lead to upgrade to CRT pacing in these patients. In 2 cases, we upgraded to CRT pacing using a conventional DDD pacemaker and used the occasion to re-implant the ventricular leads due to a lead failure. The other 8 patients had electrical dyssynchrony during intrinsic conduction. Of those, 3 patients who were included in the sLV group had right bundle branch block with a pulmonary ventricle. The other 5 patients had right bundle branch block with a systemic RV (sRV group) or an inadequate atrio-ventricular conduction disturbance with heterotaxy syndrome with an unbalanced systemic bi-ventricle (sBV). The majority of our patients (60%) had ventricular dyssynchrony associated with single-site ventriculography units with filming speeds of 30 frames · s⁻¹, were used. To ensure valid measurements, ectopic or post-ectopic beats were avoided.

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There were 3 patients in the sLV group with a double inlet LV after a ventricular septation who had already been implanted with, or indicated for, a permanent pacemaker. In those cases, the inter-ventricular septum could not actively contract but contracted passively. In the sBV group, 4 out of 6 cases had heterotaxy syndrome and were not indicated for a bi-ventricular surgical correction. In the sRV group, 5 out of 7 cases had a congenitally or surgically corrected transposition of great arteries with a systemic RV.

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Figure 1. Two unbalanced ventricles were synchronized in order to place both ventricles in the horizontal direction (A) in the sBV group. In 3 of the sBV patients who had a large RV as the main chamber, dual site pacing was performed between the RV apex and RV outflow beneath the aorta and in the (B) longitudinal direction. In the sRV group, dual site pacing was performed between the RV apex and RV outflow (C). sBV, unbalanced 2 ventricles as a single ventricular physiology; RV, right ventricle.

Figure 2. Acute impact of the cardiac resynchronization therapy (CRT). In the acute hemodynamic study, the QRS duration (A), peak +dP/dt (B) and central venous pressure (CVP) (C) significantly improved with the dual site pacing. End-diastolic pressure (EDP) (D).
had a QRS duration that did not shorten and the sysV peak +dP/dt improved with dual site ventricular pacing. We then implanted the CRT device system based on the findings of this acute hemodynamic study. Subsequently, dual site pacing had a beneficial effect on the heart rates and shortened the QRS duration in this patient with atrial fibrillation.

**Chronic Impact of CRT**

Fifteen patients treated with CRT pacing underwent cardiac catheterization to evaluate the chronic impact on the sysV volume reduction. Before the catheterization, we adjusted the atrio-ventricular pacing delay using echocardiography, as advocated by Ishikawa et al. The CRT treatment settings, such as the pacing interval between 2 ventricular pacing sites, were concurrently optimized. Figure 3 shows the chronic impact of CRT on the sysV volume, BNP level, and NYHA functional class. The ventricular volume index decreased significantly from 139±41 to 118±33 ml/m² (P=0.04) after CRT pacing, and there was a significant improvement in the BNP level (from 341±384 to 160±152 pg/ml, P=0.01) and NYHA functional class (from 2.1±0.6 to 1.8±0.7, P=0.02) at approximately 6 months after the device implantation. Moreover, the ventricular volume decreased as a chronic effect of the CRT pacing in patients with CHD.

**Impact of the sysV Morphology on the Chronic Effects of CRT**

We also evaluated the influence of the ventricular morphologies on the chronic effect. The QRS duration was significantly shortened, both in the acute hemodynamic study and 6 months after the CRT, compared to the baseline values in all 3 groups (Figure 4A). However, although the EDVI and sysV-EF significantly improved in the sLV and sBV groups, no improvement was observed in the sRV group (P<0.01; Figures 4B, C). To compare the chronic impact of CRT among the 3 different sysV morphologies, we performed multiple comparisons on the values of the QRS duration ratio (post QRS/pre QRS), EDVI ratio (post EDVI/pre EDVI), and...
EF ratio (post EF/pre EF). Although, there was a significant difference between the sLV and sRV on the values of the EDVI ratio by the post-hoc analysis, there was no significant difference between the sBV and sRV. There was no significant difference in either the QRS duration ratio or EF ratio among the 3 groups.

Mortality
Two of the 19 (10%) patients died during the follow up after the CRT device implantation. The cause of death was perioperative mortality in 1 case (conversion to total cavopulmonary connection; TCPC). In this case, the CRT device system was implanted at the time of the TCPC conversion. The indication for this surgery was mainly a low cardiac output due to ventricular dyssynchrony between the LV and RV as a systemic bi-ventricle. In the other case, death was due to interstitial pneumonitis associated with the use of amiodarone for frequent episodes of supraventricular tachycardia and syncope.

Discussion
We have described the acute and chronic impact of CRT in patients with CHD. We implanted a CRT pacing system based on shortening of the QRS duration with improved sysV performance during the acute hemodynamic study. A ventricular volume reduction was achieved with CRT pacing in the sLV group. CRT pacing using conventional methods did not result in a favorable response in patients with a sRV despite significant shortening of the QRS duration. In cases with a sBV, the 2 unbalanced ventricles have a systemic ventricular function. Therefore, anatomic interventricular dyssynchrony also results in functional intra-ventricular dyssynchrony, and biventricular pacing could greatly improve the dyssynchrony and hemodynamics in such cases. The sLV group responded well to CRT, similar to patients with chronic heart failure with a structurally normal heart. However, CRT pacing did not result in a favorable response in patients with a sRV despite significant shortening of the QRS duration.

Several studies have reported on the efficacy of CRT for CHD patients. Although, in these studies, the primary endpoint was not a ventricular volume reduction but an improvement in the functional status. In our series, the functional status improved even in the sRV group. We believe that there may be differences in the response to CRT treatment among CHD patients in various hemodynamic settings, particularly those with systemic ventricular morphologies. Our data showed that the sLV patients responded better to the CRT than the sRV patients within the meaning of a ventricular volume reduction.

These different responses of the sLV and sRV to CRT are due to the multifactorial mechanisms of sRV failure. First, the sRV patients have myocardial damage caused by repeated surgeries. Second, the morphological aspects, including the geometry of the RV, make it more suited to handle a volume overload and less suited to handle the constant pressure overload of the systemic circulation. Furthermore, physiological processes are very important; a RV pressure overload causes ventricular hypertrophy, which reduces the myocardial capillary density and flow reserve. This creates demand ischemia, which further deteriorates the function of the systemic RV. Such mechanisms of sRV failure eventually lead to myocardial fibrosis, to which late sRV dysfunction is related, and the extent of fibrosis correlates with the electrophysiological parameters. These features of sRV failure are similar to those of ischemic cardiomyopathy or end-stage cardiomyopathy. In fact, the MIRACLE study showed that the benefits of CRT with respect to the EF and reverse remodeling were greater in patients with non-ischemic heart failure than ischemic heart failure. Moreover, as Vidal et al described, CRT non-responder patients have a more advanced stage of cardiomyopathy.

Although therapeutic options for patients with LV failure are well-established, their role in the treatment of patients with sRV failure is unclear. Results of studies on the effects of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and β-blockers have been mixed; some have demonstrated a significant improvement and others have not. Our data on the poor response to CRT pacing for sRV patients are analogous to the effect of medical treatments for congestive heart failure in sRV patients. We do not yet know the pacing sites that are optimal for a systemic RV. Resynchroni-

Figure 4. Impact of the cardiac resynchronization therapy (CRT) on the QRS duration and systemic ventricle (sysV) function among the 3 sysV morphologies. The rectangle indicates the left ventricle sysV (sLV), the circle indicates the unbalanced sysV single ventricle physiology (sBV), and the triangle indicates the right ventricle sysV (sRV) group. (A) QRS duration before the CRT with dual site pacing and ≥6 months after the CRT treatment; (B, C) The sysV end-diastolic volume index (EDVI) and ejection fraction (EF) before and after the CRT treatment in the 3 groups.
zation of the systemic RV while considering the degeneration of the myocardium, geometry and mechanism of contraction, is a direction for future study. The evaluation of fibrosis using cMRI might help us to avoid placing epicardial ventricular leads on highly degenerated areas. With regard to the geometry of the RV, resynchronization of the sRV might have to be performed in a longitudinal (apex to outflow) rather than a horizontal direction.

Study Limitations
One limitation to this study was the small number of patients. In addition, the heterogeneity of the ventricular morphology did not facilitate the evaluation of accurate echocardiographic parameters that would suggest ventricular dyssynchrony; in the present study, dyssynchrony was defined based on the presence of a QRS duration ≥130 ms and dyssynchronized ventricular motion, as viewed in cine-angiography and echocardiography. The third limitation was the inaccurate assessment of the cardiac function and ventricular volume, especially of a non-LV-type systemic ventricle, in terms of the EDVI and EF; other modalities, such as cMRI, would have improved the accuracy; however, the technique was contraindicated in patients who had undergone a device implantation.

Conclusions
CRT pacing improved the electrical dyssynchrony in patients with CHD. In patients with a sLV and sBV, a ventricular volume reduction was achieved by CRT pacing. However, patients with a sRV did not respond as well as the sLV/sBV patients to CRT pacing. Although CRT pacing might be able to correct one of the exaceriating factors of heart failure in CHD patients, resynchronization of the sRV will require a new approach.

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