Biventricular pacing (BVP) has recently been proposed for treating patients with drug-refractory heart failure and intraventricular conduction delay. The potential mechanisms for improvement include restoration of left ventricular (LV) septal mechanical synchrony, reduction in pre-systolic mitral regurgitation and optimization of diastolic function, with optimization of diastolic filling time.1,2 The MIRACLE study reported that cardiac resynchronization using BVP results in significant clinical improvement in patients with chronic heart failure (CHF),3 however, there is no evidence of improvement in sympathetic nerve activity (SNA).4

**Methods and Results** Eighteen patients with CHF (dilated cardiomyopathy/ischemic cardiomyopathy =14/4) and left ventricular (LV) ejection fraction <40%, QRS duration >160 ms and dyssynchronous LV wall motion were classified into 2 groups based on the findings of 99mTc-methoxyisobutyl isonitrile (MIBI) quantitative gated single-photon emission computed tomography (SPECT) (QGS). Resynchronization was considered to be present when the difference between the QGS frame number for end-systole for the LV septal and lateral walls (dyssynchrony index) disappeared. Group A achieved resynchronization after BVP, but not Group B. In group A, New York Heart Association functional class (p=0.0002), specific activity scale (p=0.0001), total defect score (p<0.05), and the heart/mediastinum ratio of delayed 123I-metaiodobenzylguanidine imaging (p<0.05) were significantly improved after resynchronization. However, there was no significant change in group B.

**Conclusions** Cardiac resynchronization after BVP can improve cardiac symptoms, exercise capacity, and SNA in patients with moderate to severe CHF. **(Circ J 2006; 70: 703–709)**

**Key Words:** Biventricular pacing; Cardiac sympathetic nerve activity; Dyssynchrony index; 123I-MIBG imaging; 99mTc-MIBI imaging

and therefore improved cardiac symptoms and function in patients with CHF. SNA evaluated by 123I-metaiodobenzylguanidine (MIBG) imaging was reported to be useful in estimating the severity of CHF and the prognosis in patients with CHF.5,6 Recently introduced quantitative gated single-photon emission computed tomography (SPECT) (QGS) software allows visualization of LV wall motion as well as calculation of LV volume throughout the cardiac cycle using an automatic edge detection algorithm.7–13 We have determined that LV wall motion resynchronization after BVP can be assessed by evaluating regional wall motion using 99mTc-methoxyisobutyl isonitrile (MIBI) QGS. The purpose of this study was to assess whether cardiac symptoms, function, exercise capacity, and cardiac SNA improve in CHF patients who achieve resynchronization after BVP.

**Methods**

**Patients**

Eighteen patients with moderate to severe CHF, (dilated cardiomyopathy (DCM)/ischemic cardiomyopathy (ICM) = 14/4, male/female = 16/2, age = 68±7 years) were included in this study. All patients had a LV ejection fraction (LVEF) <40%, QRS interval >160 ms, and dysynchronous LV wall motion. All patients received appropriate treatment for congestive heart failure, which included diuretics, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers and β-blockers. The doses of these medications had been unchanged for at least 3 months. At the time of...
pacemaker implantation, 16 patients were in sinus rhythm and had left bundle branch block; the other 2 patients were in chronic atrial fibrillation without pacemaker implantation. Patients were excluded if they already had a pacemaker or cardioverter defibrillator, if they had had a cardiac or cerebral ischemic event within the previous 3 months, or an atrial arrhythmia within the previous month. In addition, patients did not participate if their systolic blood pressure $\geq 170$ or $\leq 80$ mmHg, a heart rate $\geq 140$ beats/min, serum creatinine concentration $>3.0$ mg/dl, or serum aminotransferase activities more than 3-fold the upper limit of normal.

Nine patients who achieved resynchronization after BVP comprised group A (resynchronization group) and the remaining 9 patients comprised group B (no resynchronization group), which included 7 patients who did not achieve resynchronization after BVP and 2 patients who did not receive BVP.

Study Protocol

We performed a series of examinations including $^{123}$I-MIBG scintigraphy and $^{99m}$Tc-MIBI QGS prior to the patients undergoing BVP and after 1 year of treatment. BVP was performed with 3 transvenous leads. The right atrial lead was placed in the right atrial appendage, the right ventricular lead was placed in the right ventricular apex, and the LV lead was placed in a lateral or anterolateral or posterolateral coronary vein through the coronary sinus.

$^{123}$I-MIBG and $^{99m}$Tc-MIBI QGS Imaging

The $^{123}$I-MIBG and $^{99m}$Tc-MIBI isotopes were obtained commercially (Daiichi Radioisotope Laboratories, Chiba, Japan). The patients were injected intravenously with 111 MBq of $^{123}$I-MIBG while upright. Anterior planar and SPECT images were acquired 15 min after injection and repeated 4h later. SPECT imaging was performed using a
Table 1 123I-MIBG and 99mTc-MIBI Data

<table>
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<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age (years)</th>
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<th>Rhythm</th>
<th>PVC</th>
<th>BVP</th>
<th>ACE</th>
<th>ARB</th>
<th>Diur</th>
<th>TDS (123I-MIBG)</th>
<th>H/M ratio</th>
<th>Washout rate</th>
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<tr>
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<td>–</td>
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<td>50.3</td>
<td>46.6</td>
<td>9.3</td>
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</table>

Group B (no resynchronization group)

| 1           | M      | 61          | DCM      | SR     | +   | +   | +   | –   | +   | 34            | 44        | 1.57         | 1.65            |
| 2           | M      | 68          | DCM      | SR     | –   | +   | –   | +   | –   | 37            | 43        | 1.89         | 1.47            |
| 3           | M      | 72          | DCM      | SR     | –   | +   | +   | –   | +   | 41            | 30        | 1.61         | 1.56            |
| 4           | M      | 69          | DCM      | AF     | +   | +   | +   | –   | +   | 19            | 29        | 1.98         | 1.60            |
| 5           | M      | 65          | DCM      | SR     | –   | +   | +   | –   | +   | 29            | 27        | 1.48         | 1.51            |
| 6           | M      | 77          | ICM      | SR     | –   | –   | –   | –   | +   | 53            | 53        | 1.32         | 1.22            |
| 7           | M      | 72          | DCM      | SR     | +   | –   | +   | –   | +   | 18            | 48        | 1.65         | 1.31            |
| 8           | M      | 82          | DCM      | SR     | –   | +   | –   | –   | +   | 41            | 32        | 1.32         | 1.65            |
| 9           | F      | 63          | DCM      | SR     | –   | +   | +   | –   | +   | 40            | 28        | 1.80         | 1.97            |
| Mean        |        |             |          |        |     |     |     |     |     | 34.7          | 37.1       | 1.62         | 1.55            |
| ±SD         |        |             |          |        |     |     |     |     |     | 46.9          | 49.4       | 15.3         | 17.3            |

*p<0.05 vs BSL.
PVC: premature ventricular contractions; BVP: biventricular pacing; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; Diur: diuretics; TDS: total defect score; BSL: baseline; 1y: year 1 of the study; H/M: heart-to-mediastinum; ICM: ischemic cardiomyopathy; SR: sinus rhythm; DCM: dilated cardiomyopathy; AF: atrial fibrillation.

99mTc-MIBI QGS

QGS was performed before and after treatment. SPECT images were acquired for 50 s in 5° increments over a 360° orbit. Acquisitions were gated for 16 frames per cardiac cycle. The total acquisition time was 16 min. Commercial QGS software with a temporal resolution of 16 frames per RR interval was used to create a 3-dimensional surface cinemode display, which was used for the evaluation of wall motion, as well as the calculation of the LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF using an automatic edge detection algorithm. We also calculated the dyssynchrony index (DSI), which was defined as the difference in the number of frames showing the maximum systolic movement of the LV septal and lateral walls in the left anterior oblique projection (Fig 2). We defined achievement of resynchronization by the absence of a difference in the number of frames (DSI=0) in the left anterior oblique projection of the QGS. Two experienced observers who were unaware of the clinical status of the patients and the results of BVP visually assessed the DSI and TDS of the 123I-MIBG and 99mTc-MIBI images. A third reviewer was consulted in cases of disagreement.

Cardiac Symptoms and Exercise Capacity

Cardiac symptoms were scored using the New York Heart Association (NYHA) functional classification. Exercise capacity was estimated using specific activity scale (SAS). We asked all patients 21 questions at the beginning of the study and 1 year later and estimated exercise capacity.

Statistical Analysis

All data are expressed as the mean ± SD. Unpaired t-tests were used to compare differences between the groups as

dedicated 3-detector imaging system (PRISM 3000; Picker International, Cleveland, OH, USA). The detectors were corrected constantly for energy, uniformity and linearity. Projection images were acquired for 55 s in 5° increments over 360° orbits and were recorded at a digital resolution of 64×64 pixels. Immediately after this acquisition, the patients were injected with 720 MBq of 99mTc-MIBI and then the 99mTc-MIBI imaging was acquired in an upright position 30 min later. 99mTc-MIBI gated images were acquired for 50 s in 5° increments over 360° orbits. Energy discrimination was provided by a 20% window around the 159-keV photopeak of 99mTc-MIBI. Using the anterior planar delayed 123I-MIBG images, the heart-to-mediastinum (H/M) activity ratio was obtained using regions of interest placed over the heart (H) and upper mediastinum (M). The washout rate was calculated using the formula (H-M)early−(H-M)delayed/(H-M)early×100. The myocardial SPECT image set for each patient was divided into 20 segments (Fig 1). The short-axis images from the basal, middle, and apical ventricular levels were divided into 6 segments. The apical segment of the vertical long-axis image was divided into 2 segments. Regional tracer uptake was scored semiquantitatively using a 4-point scoring system (0=normal uptake; 1=mildly reduced uptake; 2=moderately reduced uptake; 3=severely reduced uptake or defect). The total defect score (TDS) of the 123I-MIBG and 99mTc-MIBI images was calculated as the sum of the scores for all 20 segments.

99mTc-MIBI QGS

QGS was performed before and after treatment. SPECT images were acquired for 50 s in 5° increments over a 360° orbit. Acquisitions were gated for 16 frames per cardiac cycle. The total acquisition time was 16 min. Commercial QGS software with a temporal resolution of 16 frames per RR interval was used to create a 3-dimensional surface cinemode display, which was used for the evaluation of wall motion, as well as the calculation of the LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF using an automatic edge detection algorithm. We also calculated the dyssynchrony index (DSI), which was defined as the difference in the number of frames showing the maximum systolic movement of the LV septal and lateral walls in the left anterior oblique projection (Fig 2). We defined achievement of resynchronization by the absence of a difference in the number of frames (DSI=0) in the left anterior oblique projection of the QGS. Two experienced observers who were unaware of the clinical status of the patients and the results of BVP visually assessed the DSI and TDS of the 123I-MIBG and 99mTc-MIBI images. A third reviewer was consulted in cases of disagreement.

Cardiac Symptoms and Exercise Capacity

Cardiac symptoms were scored using the New York Heart Association (NYHA) functional classification. Exercise capacity was estimated using specific activity scale (SAS). We asked all patients 21 questions at the beginning of the study and 1 year later and estimated exercise capacity.

Statistical Analysis

All data are expressed as the mean ± SD. Unpaired t-tests were used to compare differences between the groups as
appropriate. Paired t tests were used to compare differences between each variable before and after treatment. Linear regression analysis was used to analyze the relationship between the change in DSI and cardiac symptoms, function, exercise capacity, and SNA. A p-value <0.05 was considered significant. Delta (Δ) represents the change in a value and means the improved degree of value.

Results

Changes in SNA (Table 1)

In group A, the TDS of the delayed 123I-MIBG image significantly decreased after 1 year of treatment (35.7±8.0) compared with the baseline value (42.7±11.2, p<0.05, Fig 3). However in group B, there was no significant change after 1 year of treatment. The ΔTDS of the delayed 123I-MIBG did not change significantly between the 2 groups (p=0.08). In group A, the H/M ratio of the delayed 123I-MIBG images significantly increased after 1 year of treatment (1.56±0.23) compared with the baseline value (1.40±0.28, p<0.05, Fig 4). In group B, there was no significant change after 1 year of treatment. The ΔH/M ratio of the delayed 123I-MIBG images in group A was 0.15±0.19, which was significantly higher than that for group B (–0.08±0.25, p<0.05). There was no significant change in the washout rate for 123I-MIBG images after 1 year of treat-
ment in either group. There was no significant change in the ∆washout rate for 123I-MIBG images in either group.

The TDS and the H/M ratio of 123I-MIBG images are relative evaluations in patients with low uptake by the heart. We examined whether there was reproducibility using paired t-tests. From the acquired raw data of 123I-MIBG at baseline and after 1 year of treatment, we calculated the H/M ratio, constituted the SPECT image, calculated the TDS again, and compared them. There was no significant difference between the baseline H/M (1.52±0.28 vs 1.51±0.27), after 1 year of treatment (1.55±0.22 vs 1.55±0.22), the baseline TDS (38.7±11.6 vs 38.8±11.9) and after 1 year of treatment (36.4±8.8 vs 36.6±8.8). We considered that the TDS and the H/M ratio of the 123I-MIBG images were reproducible.

Myocardial Perfusion (Table 1)
There was no significant change in the TDS for the 99mTc-MIBI images in either group after 1 year of treatment. There was no significant change in ∆TDS of 99mTc-MIBI images in either group.

Changes in Cardiac Function (Table 2)
There was no significant change in LV function (LVEF, LVEDV and LVESV) in either group after 1 year of treatment, nor was there significant change in ∆LVEF, ∆LVEDV, or ∆LVESV.

Changes in Cardiac Symptoms and Exercise Capacity (Table 2)
In group A, the NYHA class significantly improved after 1 year of treatment (2.3±0.7) compared with the baseline value (3.4±0.5, p=0.0002, Fig 5). In group B, however there was no significant change after 1 year of treatment. In group A, the SAS measurement significantly increased after 1 year of treatment (4.0±1.8) compared with the baseline value (1.9±1.5, p=0.0001), but there was no significant change in group B. The ∆SAS of group A (2.1±0.8) was significantly greater than that of group B (0.0±1.2, p<0.001, Fig 6).

Changes in DSI (Table 2)
In group A, the DSI significantly decreased after 1 year of treatment (0±0) compared with the baseline value (5.0±2.2, p<0.0001), but there was no significant change in group B. There was a significant correlation between the ∆DSI and ∆EF in group A (r=0.75, p<0.05, Fig 7), but none in group B.

During follow up, 4 patients in group B required hospi-
talization because of worsening heart failure, whereas only 1 patient in group A required hospitalization for this reason.

Fig 8 (Upper panel) shows an example of the 123I-MIBG uptake after treatment in group B. There was significant low-level uptake in the inferior and apical walls before treatment, but no significant change after treatment. The H/M decreased from 1.61 to 1.56 and the LVEF did not change (23% to 23%) after treatment. Fig 8 (Lower panel) shows an example of 123I-MIBG uptake after treatment in group A. There was significant low-level uptake in the inferior and apical walls before treatment and the uptake in the inferior wall increased slightly after treatment. The H/M increased from 1.33 to 1.63 and the LVEF increased from 17% to 29% after treatment.

Discussion

Myocardial scintigraphy with 123I-MIBG, an analog of norepinephrine, provides images that reflect cardiac sympathetic nerve function. The uptake of 123I-MIBG is considered useful for the evaluation of the severity of heart failure and in addition, the H/M ratio and TDS of the delayed 123I-MIBG images correlate with the LVEF. 123I-MIBG can be used to also determine prognosis and evaluate therapeutic efficacy. Cardiac 123I-MIBG activity has the most powerful independent long-term prognostic value for both ICM patients and idiopathic cardiomyopathy patients, indicating that both disease processes have common pathophysiologic and prognostic implications of impaired cardiac sympathetic innervation.

Cardiac resynchronization therapy reduces the degree of ventricular dyssynchrony as evidenced by a decrease in the duration of the QRS interval; this effect is accompanied by an increase in the LVEF, and a decrease in the LV end-diastolic dimension, and a decrease in the magnitude of mitral regurgitation. Nelson et al demonstrated that BVP rapidly improves systolic function while modestly reducing myocardial oxygen consumption. Sander et al demonstrated that patients with ICM or DCM both responded to cardiac resynchronization therapy and the underlying etiology of heart failure (ICM vs DCM) was not related to the response to cardiac resynchronization therapy.

The results of the present study indicate that cardiac resynchronization therapy improves not only cardiac symptoms and exercise capacity, but also cardiac SNA in patients with moderate to severe CHF and a prolonged QRS interval. Compared with the patients who did not achieve cardiac resynchronization after BVP or who did not receive BVP, those who achieved cardiac resynchronization after BVP had a significant improvement in cardiac symptoms, exercise capacity and cardiac SNA, as estimated by the H/M ratio and TDS of delayed MIBG imaging. Based on our results, we believe that cardiac resynchronization therapy contributes to improved cardiac SNA. Previous studies have shown that cardiac function in patients with CHF improves after cardiac resynchronization; although in this study it did not significantly improve after cardiac resynchronization. The LVEF was almost the same after treatment in both groups. However, there is a significant correlation in the degree of improvement between LVEF and the DSI. LVEF may improve if there is a bigger improvement in the degree of dyssynchrony. Furthermore, in the no resynchronization group the LV lead may have been in a suboptimal position, or become dislodged during long-term pacing, or was pacing non-viable myocardium of the septal or lateral wall. Cardiac resynchronization therapy contributed to an improvement in cardiac SNA as well as cardiac symptoms and exercise capacity. Cardiac SNA improved significantly in patients who had achieved synchrony after BVP. In addition, there was not significant correlation between the degree of improvement in perfusion (∆TDS of 99mTc-MIBI) and SNA (∆TDS, H/M ratio...
and WR of $^{123}$I-MIBG).

Tissue Doppler imaging has become a very popular method of evaluating ventricular dyssynchrony.\(^2\) It enables assessment of interventricular dyssynchrony, which is especially relevant with new generation devices that allow for LV/right ventricular offset optimization.\(^3\) However, the results are influenced by the physique of the patient and may depend on the skill of the operator. On the other hand, the QGS method is operator independent and highly reproducible, and can provide accurate information on both LV function/dimensions and perfusion, even in patients with LV dysfunction.\(^4\) In this study, we easily assessed LV synchrony and wall motion, as well as LV function. Therefore, we believe that QGS is a useful technique in the assessment of LV synchrony, as well as LV function in patients receiving BVP.

**Study Limitations**
Because of the relatively small number of patients in this study, it was difficult to assess differences between the resynchronization and no resynchronization groups. Because of the small number of patients who did not receive BVP, we could not compare patients receiving BVP with those who did not receive BVP. In addition, because LV synchrony was assessed using 16 frames per cardiac cycle and the interval of the frames was determined by heart rate chrony was assessed using 16 frames per cardiac cycle and who did not receive BVP. In addition, because LV synchrony was assessed using 16 frames per cardiac cycle and no resynchronization groups. Because of the relatively small number of patients in this study, it was difficult to assess differences between the resynchronization and no resynchronization groups. Because of the small number of patients in this study, it was difficult to assess differences between the resynchronization and no resynchronization groups. Because of the small number of patients who did not receive BVP, we could not compare patients receiving BVP with those who did not receive BVP. In addition, because LV synchrony was assessed using 16 frames per cardiac cycle and the interval of the frames was determined by heart rate.

**Conclusion**
Achieving cardiac resynchronization after BVP will not improve cardiac function, but can improve cardiac symptoms, exercise capacity and cardiac SNA in patients with moderate to severe CHF.

**References**