Reverse Perfusion-Metabolism Mismatch Predicts Good Prognosis in Patients Undergoing Cardiac Resynchronization Therapy
— A Pilot Study —

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**Background** Cardiac resynchronization therapy (CRT) improves glucose metabolism in the septum of patients with heart failure, so in the present study the predictive value of combined fluorodeoxyglucose (FDG)-positron emission tomography (PET) and metoxy-isobutyl isonitrile (MIBI)-single photon emission computed tomography (SPECT) for the prognosis of patients undergoing CRT was investigated.

**Methods and Results** Fourteen patients (70.3±8.2 years) who underwent FDG-PET and MIBI-SPECT before implantation of a biventricular pacemaker were enrolled. The total number of matches, mismatches, reverse mismatches, summed difference score (SDS: sum total of FDG–MIBI scores) and SDS per segment (%SDS) in each of 5 areas of myocardium (septum, anterior, lateral, inferior area, apex) was calculated and compared between the survival groups (all survival: survival group; survival without ischemic heart disease (IHD): non-IHD survival group) and non-survival group. Both the number of reverse mismatch segments and the %SDS in the septum in the non-IHD survival group were significantly greater than in the non-survival group (3.2±1.6 vs 0.5±0.6, p<0.05; 0.62±0.61 vs –0.11±0.19, p<0.05). The receiver-operating characteristics curves for prognosis showed that the area under the curve for the number of reverse mismatch segments in the septum (0.93; confidence interval 0.61–0.98) was significantly greater.

**Conclusion** A reverse mismatch pattern in the septum can predict a good prognosis for patients treated with CRT. (Circ J 2007; 71: 126–131)

**Key Words:** Cardiac resynchronization therapy; FDG-positron emission tomography; Reverse perfusion-metabolism mismatch

It is now accepted that cardiac resynchronization therapy (CRT) improves cardiac function in patients with heart failure, and thus reduces morbidity and mortality. However, cardiac function does not improve in all patients who undergo CRT. Some studies have revealed the predictive ability of the response to CRT. Patients with left ventricular (LV) systolic dysfunction and dilatation frequently have ventricular conduction delay, such as left bundle branch block (LBBB), which is associated with delayed contraction of the lateral LV wall, causing early contraction of the septum, resulting in paradoxical movement. The abnormal activation sequence induced by spontaneous LBBB or by right ventricular (RV) pacing-induced LBBB influences both the perfusion and glucose metabolism of the septum. Simultaneous perfusion imaging with a tracer, such as technetium metoxy-isobutyl isonitrile (Tc-MIBI) or NH3, and fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been used to identify myocardial viability and high-risk patients who are likely to benefit from revascularization therapy. Correct interpretation of the patterns of flow and metabolism, such as match, mismatch and reversed mismatch, is important. A mismatch pattern is observed in ischemic, hibernating but viable myocardium, whereas a reverse mismatch pattern is often observed in patients with a recent myocardial infarction or chronic stable coronary artery disease or LBBB. It was recently demonstrated that a reverse mismatch pattern is a sign of reversible myocardial dysfunction.

Both spontaneous and induced LBBB show a reverse mismatch pattern in the septal myocardium, but the significance of this pattern as a predictor of prognosis in patients who subsequently undergo CRT is unknown. In this pilot study we used FDG-PET and metoxy-isobutyl isonitrile (MIBI)-single photon emission computed tomography (SPECT) to investigate whether the patterns of flow and glucose metabolism were related to prognosis in patients who underwent CRT.

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Methods

Patients

From December 2001 to April 2005, 14 patients with congestive heart failure (CHF; New York Heart Association functional class III or IV; 11 males, 3 females; mean age 70.3±8.2 years) were enrolled. The mean follow-up period was 19.5±13.7 months. The patients underwent a myocardial perfusion study with MIBI-SPECT and a metabolism study with FDG-PET before implantation of a biventricular pacemaker. The interval between FDG-PET and MIBI-SPECT was within 7 days. All patients had an LV ejection fraction (LVEF) <35%, as evaluated by echocardiography. The etiology of CHF was dilated cardiomyopathy in 11 patients and ischemic heart disease (IHD) in 3 patients.

Three patients with IHD had an old myocardial infarction. The last onset was 1.5 years or more before this study. Medications were not changed during each follow-up period, and no new coronary intervention occurred during the previous 1 year of the study. None of the patients with IHD revealed a new ischemic event on ECG or died during the follow-up period. Exclusion criteria included recent myocardial infarction and unstable angina. All patients attended follow-up visits every 3 months. Four patients died of heart failure during the follow-up. All patients were followed for more than 12 months and were divided into 2 groups: survival and non-survival. The survival group had 3 patients with IHD and 7 patients without IHD. There was no patient with IHD in the non-survival group. The survival group was further divided into 2 subgroups (all survival: survival group; survival without IHD: non-IHD survival group). We investigated the predictive value for survival: survival group; survival without IHD: non-IHD survival group. The characteristics of all groups are shown in Table 1. Written informed consent was given by each patient before the study.

SPECT

Myocardial perfusion at rest was assessed with Tc-MIBI-SPECT using a previously described protocol and a 90° dual-head camera (Millennium VG, GE, Yokokawa, Japan) equipped with a low-energy, high-resolution collimator. The tomographic data were analyzed in a 64×64 matrix and stored in a personal computer. Myocardial-gated SPECT was performed 1 h after a rest injection of 740 MBq MIBI, using a 20% symmetric energy window centered on the 140 KeV peak. The data were filtered with a Butterworth filter at a cutoff frequency of 0.4 cycles/pixel.

PET

FDG-PET imaging using a Shimadzu-SET 2,400W PET scanner (Headtome V, Shimadzu, Kyoto, Japan) was performed under glucose loading. Each patient received 75 g glucose orally 1 h before intravenous administration of FDG (370 MBq), which was given 1 h prior to image acquisition. Before obtaining gated emission images, simultaneous emission and transmission data were acquired for 15 min and were used to correct photon attenuation. Transaxial, short-axial and vertical long-axial images were reconstructed using the summed gated data. Images were collected in 128×128 matrices and then reconstructed with a Butterworth filter and a Ramp filter. Transaxial images were reconstructed using the Butterworth-filtered backprojection method (order: 2; cutoff frequency, 0.4). Horizontal long-axial, and vertical long- and short-axial images were obtained.

Data Analysis

Each patient’s SPECT and PET images of 5 areas of myocardium (septum, anterior area, lateral area, inferior area and apex) were visually interpreted by 2 clinicians. The myocardium of the left ventricle was divided into 20 segments according to previous reports and each segment

| Table 1 Comparison of Baseline Characteristics of Survival Group, Non-IHD Survival Group and Non-Survival Group |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Survival group (n=10) | Non-IHD survival group (n=7) | Non-survival group (n=4) | p value |
| Age (years) | 70.3±8.2 | 69.1±9.9 | 68.8±7.6 | NS |
| Sex (M/F) | 8/2 | 5/2 | 3/1 | NS |
| NYHA class III/IV | 9/1 | 6/1 | 3/1 | NS |
| QRS duration (ms) | 184.8±21.1 | 179.0±35.8 | 208.3±29.6 | NS |
| LVEF (%) | 27.3±6.8 | 27.3±8.3 | 33.2±2.3 | NS |
| Medication (%) | | | | |
| ß-blockers | 9/10 | 6/7 | 4/4 | |
| ACE inhibitors or AT1 receptor antagonists | 9/10 | 6/7 | 4/4 | |
| Diuretics | 5/10 | 4/7 | 4/4 | |
| Spironolactone | 6/10 | 4/7 | 4/4 | |

P values show the significance of differences between the non-IHD survival group and non-survival group. IHD, ischemic heart disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; AT1, angiotensin type 1.
was scored. FDG and MIBI images were visually assessed using a 5-point scoring system: 4 = no uptake, 3 = severe defect, 2 = moderate defect, 1 = mild defect and 0 = normal uptake. Disagreements were resolved by consensus. The pattern of myocardial metabolism and flow in each segment was defined as match, mismatch or reverse mismatch; a matched pattern was defined as similarly reduced glucose uptake and perfusion, a mismatched pattern was defined as reduced perfusion uptake relative to glucose, and a reverse mismatch was a FDG score less than the corresponding MIBI score. The total number of reverse mismatched segments, the summed difference score (SDS: sum total of FDG – MIBI scores) and SDS per segment (%SDS) in each of the 5 areas were calculated and compared between the survival groups and the non-survival group.

**Echocardiography**

We measured LVEF from M-mode images by echocardiography before CRT and approximately 3 months after CRT. Before CRT, intraventricular asynchrony was evaluated as the delay between the motion of the septum and that of the left posterior wall (septal-to-posterior wall motion delay (SPWMD); ms). It was calculated as the shortest interval between the maximal posterior displacement of the septum and the maximal displacement of the left posterior wall in M-mode images as previously described.

**Statistical Analysis**

Values are given as mean ± SD. Data were compared using paired or unpaired t-test where appropriate. Receiver-operating characteristics (ROC) curves for sensitivity and specificity were constructed to evaluate the predictive value of the studied variables, and the areas under the curve (AUC) were compared to estimate the accuracy of the variables. A p-value < 0.05 was considered significant.

**Results**

The number of reverse mismatch segments in the septum and apex was significantly different between the non-IHD

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**Table 2 Number of Reverse Mismatch Segments in Each Area of Myocardium in Survival Group and Non-Survival Group**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Etiology</th>
<th>Area of myocardium</th>
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<tr>
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<td>Non-IHD</td>
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</tr>
<tr>
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<td>Non-IHD</td>
<td>5</td>
</tr>
<tr>
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<tr>
<td>4</td>
<td>Non-IHD</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Non-IHD</td>
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<tr>
<td>6</td>
<td>Non-IHD</td>
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<tr>
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<tr>
<td>8</td>
<td>IHD</td>
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<tr>
<td><strong>Non-survival group</strong></td>
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<td>1</td>
</tr>
<tr>
<td>12</td>
<td>Non-IHD</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation see in Table 1.

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Fig 1. Number of reverse mismatch segments in each area of myocardium in non-ischemic heart disease (IHD) survival group and non-survival group.

Fig 2. Percent summed difference score (%SDS) in each area of myocardium in non-ischemic heart disease (IHD) survival group and non-survival group.
survival group and the non-survival group (3.4±1.7 vs 0.5±0.6, 1.0±0.6 vs 0.0±0.0, p<0.05) (Table 2, Fig 1). The number of reverse mismatch segments in the anterior, lateral and inferior areas showed no difference between the non-IHD survival group and the non-survival group (1.6±1.1 vs 0.5±0.6, 2.1±1.8 vs 1.3±0.5, 0.4±0.8 vs 0.0±0.0, p=NS, respectively) (Table 2, Fig 1). The %SDS in the septum in the non-IHD survival group was significantly higher than that in the non-survival group (0.62±0.61 vs −0.11±0.19, p<0.05) (Fig 2). There was no difference in the %SDS in the anterior area, lateral area, inferior area and apex between the non-IHD survival group and the non-survival group (0.76±0.81 vs 0.11±0.19, 0.50±0.81 vs 0.22±0.19, −0.57±0.85 vs −0.33±0.58, 0.57±0.67 vs 0.0±0.0, p=NS, respectively) (Fig 2). The non-IHD survival group had significantly fewer matched segments in the septum, anterior area and apex than the non-survival group (1.6±1.7 vs 4.7±1.2, 0.9±1.1 vs 2.5±0.6, 0.7±0.8 vs 2.0±0.0, p<0.05), and there was no significant difference in the lateral and inferior areas between the 2 groups (1.7±1.0 vs 2.0±0.0, 0.8±1.0 vs 1.8±1.0, p=NS, respectively). There was no

**Fig 3.** Receiver-operating characteristics curves for reverse mismatch, left ventricular ejection fraction (LVEF) and QRS duration to predict survival in the patients without ischemic heart disease.

**Fig 4.** Fluorodeoxyglucose-positron emission tomography and metoxy-isobutyl isonitrile-single photon emission computed tomography images in a case from the survival group. The patient was 79 years old, with a previous myocardial infarction in the inferior wall. Septal imaging before cardiac resynchronization therapy (CRT) showed a reverse mismatch pattern. Septal glucose metabolism was restored 2 months after CRT.
significant difference between the 2 groups in the number of mismatched segments in all segments (septum, anterior area, lateral area, inferior area and apex: 1.3±1.5 vs 1.5±1.9, 0.6±1.1 vs 0.2±0.0, 1.9±2.2 vs 0.5±0.6, 1.7±1.3 vs 1.3±1.0, 0.1±0.4 vs 0.0±0.0, p<NS, respectively).

LVEF improved significantly after CRT in the non-IHD survival group (25.6±8.1 to 37.2±9.2, p<0.05); however, it did not improve in the non-survival group (33.0±6.2 to 33.9±4.6%, p=0.62). SPWMD in the non-IHD survival group shortened significantly after CRT (135.8±123.6 ms to 4.0±5.5 ms, p<0.05), but did not change significantly after CRT in the non-survival group (17.3±18.6 ms to 16.7±28.9 ms, p=NS).

The ROC curves to predict survival in the patients without IHD showed that the AUC for the number of reverse mismatch segments in the septum (0.93; confidence interval (CI) 0.61–0.98) was greater than that for LVEF (0.66; CI 0.33–0.90) or for QRS duration (0.75; CI 0.41–0.95) (Fig.3). The number of reverse mismatch segments in the septum showed higher sensitivity than QRS duration and higher accuracy than LVEF. The specificity of the number of reverse mismatch segments was 71.4%, sensitivity 100%, and accuracy of 81.8%, whereas for QRS duration the specificity was 100%, sensitivity 42.9% and accuracy of 81.8%, and for LVEF they were 50.0%, 100% and 63.6%, respectively.

The comparison of the results for the survival group including IHD and non-survival group had a similar tendency to that of the non-IHD survival group and non-survival group. The survival group had significantly more reverse mismatch segments in the septum and apex than the non-survival group (3.3±1.5 vs 0.5±0.6, 0.8±0.6 vs 0±0.0, p<0.05). The number of reverse mismatch segments in the anterior, lateral and inferior areas showed no difference between the survival group and non-survival group (1.2±1.1 vs 0.5±0.6, 2.5±2.0 vs 1.3±0.5, 0.4±0.7 vs 0±0.0, p=NS, respectively). The %SDS in the septum was significantly higher in the survival group than in the non-survival group (0.6±0.56 vs -0.08±0.17, p<0.05). There was no difference in the %SDS in the anterior area, lateral area, inferior area and apex between the survival group and non-survival group (0.47±0.82 vs 0.11±0.19, 0.60±0.80 vs 0.22±0.19, -0.50±0.77 vs -0.33±0.58, 0.40±0.61 vs 0±0.0, p=NS, respectively). One of 3 patients with IHD showed mismatch in the septum and improved LVEF. LVEF improved significantly after CRT in the survival group (26.6±7.2% to 37.9±8.1%, p<0.05). SPWMD in the survival group shortened significantly after CRT (141.5±112.6 ms to 2.5±4.6 ms, p<0.05).

We show a representative case from the survival group in which a reverse mismatch pattern in the septum had disappeared 2 months after CRT (Fig.4).

Discussion

Our study results suggest that the severity of a reverse mismatch pattern in the septum before undergoing CRT more accurately predicts prognosis. A long-term predictor of the prognosis following CRT is not well established, although a smaller LV end-diastolic volume and more severe prepaing intraventricular asynchrony examined by tissue Doppler imaging technique with echocardiography have been reported as markers of a good response to treatment. In this study, we enrolled 3 patients with IHD, for whom we changed only the pacing method and did not add any new interventions or medications during the year before this study and following their enrollment. All the current patients had spontaneous or pacing-induced LBBB. It is known that such patients show a reverse mismatch pattern in the septum; that is, they have less glucose metabolism compared with perfusion (MIBI uptake > FDG uptake). Pacing-induced LBBB seems to affect perfusion and glucose metabolism in the septum similarly to spontaneous LBBB. The reverse mismatch pattern in patients with IHD is related closely to multivessel disease in the subacute phase of myocardial infarction. The mechanism of reverse mismatch in patients with LBBB or pacing-induced LBBB seems to be different to that in patients with IHD. With regard to the pathophysiology of reverse mismatch, it has been reported that such regions in patients with coronary artery disease are mixtures of fibrotic and reversible ischemic myocardium. LBBB in patients with severely reduced LV function shows early contraction of the septum, resulting in paradoxical movement and septal reverse mismatch phenomenon. It is supposed that a septal reverse mismatch phenomenon is related to paradoxical movement, resulting in deterioration of LV function. There are some hypotheses for the mechanism of reverse mismatch. One is that the reduced FDG uptake may relate to increased intramyocardial pressure in the septum during diastole. An experimental study showed that early septal contraction in LBBB reduced septal workload, which would lead to diminished glucose metabolism. The relationship between workload and glucose metabolism is thought to be as follows. Glucose uptake is mediated by the glucose transporter, GLUT-4, which is an insulin-sensitive transporter in the cell membrane. In an animal study, the expression of cellular GLUT-4 was increased or decreased according to myocardial workload. Nowak et al suggested that restoration of septal glucose uptake after CRT, as reflected by FDG uptake, was in accordance with an increase of GLUT-4 because of the increase in workload. In a previous report, glucose metabolism in the septum improved with less alteration in perfusion subsequent to CRT, so the restoration of glucose metabolism after CRT may be caused by an alteration in septal workload, and not by restoration of perfusion. The mechanism of the reverse mismatch in LBBB may be the result of reduced septal workload with reduced expression of GLUT-4.

A relation of LVEF and intraventricular synchrony has been shown; that is, RV pacing resulted in intraventricular asynchrony and caused a decrease in LVEF. On the other hand, it has been demonstrated that CRT improved intraventricular synchrony. The marked difference in the time to peak regional sustained systolic contraction between the septal segment and the lateral segment before CRT was abolished after CRT. It was also shown that SPWMD resulting from intraventricular asynchrony significantly improved with a reduction in LV end-systolic volume index by CRT and that ventricular asynchrony can predict a better outcome in patients with chronic heart failure undergoing CRT. LBBB or RV pacing causes intraventricular asynchrony and results in a reduction of septal workload. The survival group and the non-IHD survival group had more segments with a reverse mismatch pattern than did the non-survival group, because FDG uptake was reduced according to the reduction of septal workload. We consider that the degree of reverse mismatch pattern in the septum may correlate with the severity of intraventricular asynchrony in patients with spontaneous LBBB or pacing-induced...
LBBB, and that CRT restores septal workload. Therefore, a reverse mismatch pattern in the septum predicts a good prognosis.

**Study Limitations**

We performed FDG-PET and MIBI-SPECT before biventricular pacemaker implantation in a small number of patients. Further studies with a large number of patients are needed to demonstrate the severity of a reverse mismatch pattern as a predictor for patients who undergo CRT. The number of patients with IHD was very small and we treated the data of the patients with IHD as supplementary. Our study population had complete left bundle branch block (CLBBB) or RV pacing, so we cannot exclude the possibility that the difference in ventricular conduction patterns might contribute to outcome. It is unknown whether there is difference in the prognosis between patients with CLBBB and patients with RV pacing. Further studies with a large number of patients with the same electrophysiologic characteristics are needed to clarify the clinical significance of reverse mismatch pattern in the septum.

**Conclusion**

The number of reverse mismatch segments in the septum in survival patients was greater than that in non-survival patients. A reverse mismatch pattern in the septum of patients with spontaneous or pacing-induced LBBB may predict a good prognosis after implantation of a biventricular pacemaker.

**References**


