Noninvasive identification of anthracycline cardiotoxicity: Comparison of $^{123}$I-MIBG and $^{123}$I-BMIPP imaging

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To test the feasibility of myocardial $^{123}$I-MIBG and $^{123}$I-BMIPP imaging for the early detection of anthracycline cardiotoxicity, 13 patients who had received anthracycline anticancer chemotherapeutic agents were studied. Two-dimensional echocardiography and myocardial imaging with both $^{123}$I-MIBG and $^{123}$I-BMIPP were performed in 13 patients treated with anthracycline (group A) and 10 normal control subjects (group C). Anterior myocardial images were obtained 15 minutes and 3 hours after the injection of isotopes. The heart-to-mediastinum ratio (H/M ratio) was used to quantify cardiac $^{123}$I-MIBG and $^{123}$I-BMIPP uptake. The left ventricular shortening fraction (%SF) and the ratio of peak mitral flow velocity in early diastole to that at the time of atrial systole (E/A ratio) were measured by echocardiography. The H/M ratio of $^{123}$I-MIBG was lower in group A than in group C (1.5 ± 0.2 vs. 1.9 ± 0.2, p < 0.01). The patients in group A had faster clearance of $^{123}$I-MIBG from the myocardium than those in group C (27 ± 10% vs. 22 ± 4%, p < 0.05). However, the H/M ratio and clearance of $^{123}$I-BMIPP were similar between the two groups (H/M ratio: 2.1 ± 0.2 vs. 2.0 ± 0.2, clearance: 24 ± 6% vs. 26 ± 6%). The %SF (37 ± 8% vs. 36 ± 7%) and E/A ratio (1.4 ± 0.4 vs. 1.6 ± 0.3) were comparable in groups A and C.

The present findings indicated that myocardial imaging with $^{123}$I-MIBG could detect myocardial damage in patients treated with anthracycline in the early stage when cardiac systolic and diastolic function was still preserved. Early detection of anthracycline cardiotoxicity by $^{123}$I-MIBG would reduce the incidence and severity of heart failure.

Key words: $^{123}$I-MIBG, $^{123}$I-BMIPP, doxorubicin cardiotoxicity

INTRODUCTION

Anthracycline class chemotherapeutic agents are effective in treating hematological malignancies as well as solid tumors. Its administration, however, is limited by a dose-related cardiotoxicity that may lead to congestive heart failure, which is frequently fatal.1-3 Although numerous noninvasive methods, including electrocardiography,4 chest x-ray, echocardiography,5,6 and radio-nuclide ventriculography,7-10 have been used to detect anthracycline-induced cardiotoxicity, they had only limited value in predicting cardiotoxicity and cardiac dysfunction. Evident congestive heart failure is a late manifestation of myocardial damage, and it has been established that a large proportion of patients with normal cardiac function are at risk of congestive heart failure.11 Histopathologic changes precede clinical cardiotoxicity, and endocardial biopsy is now considered the most reliable method for detecting anthracycline-induced myocardial damage.12 However, endocardial biopsy is invasive and is not acceptable for the repeated examination. Therefore, a practical noninvasive method for monitoring anthracycline-induced myocardial damage has long been desired.

The development of radioiodinated metaiodobenzylguanidine (MIBG), an analog of norepinephrine, has allowed a study of the cardiac adrenergic nervous system in vivo.13 The MIBG kinetics in the myocardium has been shown to reflect cardiac adrenergic neuron integrity and
function.\textsuperscript{14,15} Recently, Wakasugi et al. have reported that \textsuperscript{123}I-MIBG scintigraphy is useful for the detection of adriamycin cardiomyopathy in rats.\textsuperscript{16,17} However, the application of this radiopharmaceutical has not been confirmed in clinical trials.

Iodine-123 beta-methyl-iodophenyl-pentadecanoic acid (\textsuperscript{123}I-BMIPP) has been developed as a tracer for myocardial fatty acid metabolism.\textsuperscript{18,19} Fatty acids are known to account for more than 90% of myocardial energy requirements at rest under normal fasting aerobic conditions.\textsuperscript{20} Wakasugi et al. have recently shown that myocardial substrate utilization, including fatty acids, is changed in adriamycin-induced cardiomyopathic rats.\textsuperscript{21} However, metabolic states of the myocardium in patients treated with anthracycline have not been rigorously examined.

The aim of the present study was to determine whether myocardial imaging with \textsuperscript{123}I-MIBG and \textsuperscript{123}I-BMIPP could identify the myocardial damage in patients treated with anthracycline anticancer chemotherapeutic agents.

**MATERIALS AND METHODS**

**Subjects**

Thirteen patients with malignant neoplasms who had been previously treated with anthracycline anticancer agents were studied. These were 8 males and 5 females aged 23 to 71 years (mean 53 years). The control group was composed of 10 normal subjects (6 male and 4 female) aged 28 to 66 years (mean 45 years). The etiology of the primary neoplasms and cumulative doses of anthracycline agents in treated patients are shown in Table 1. Because the objective was to evaluate asymptomatic anthracycline treated patients, patients with congenital heart disease, heart failure and arrhythmias were excluded. The time elapsed since the last dose of anthracycline therapy ranged from 4 to 12 weeks (mean 5.6 week).

**Myocardial imaging of \textsuperscript{123}I-MIBG and \textsuperscript{123}I-BMIPP**

*Study protocol:* Myocardial imaging with \textsuperscript{123}I-MIBG and echocardiography were performed on the same day in all subjects. Myocardial imaging with \textsuperscript{123}I-BMIPP was performed within one week following the \textsuperscript{123}I-MIBG studies (3 to 7 days). All patients were not received the anticancer chemotherapeutic agents between the two imaging.

*Image acquisition:* After an overnight fast, a dose of 111 MBq of \textsuperscript{123}I-MIBG or \textsuperscript{123}I-BMIPP was administered intravenously with the resting supine position. Anterior projection images were obtained 15 minutes and 3 hours after injection. A large field-of-view gamma camera (Siemens, ZLC-7500 DIGITRAC) equipped with a parallel hole, high resolution collimator was used. Each image accumulated for 10 minutes. The data were stored on a 256 × 256 matrix. Data processing was performed by a nuclear medicine computer (Shimadzu, Scintipac 700).

**Data analysis:** Square regions of interest (12 × 12 pixels in size) were defined for areas of the left ventricular myocardium with the peak count density. Another ROI (20 × 20 pixels in size) was placed over the upper mediastinum area. The heart-to-mediastinum ratio (H/M ratio) was calculated to quantify cardiac \textsuperscript{123}I-MIBG or \textsuperscript{123}I-BMIPP uptake as a fraction of the mean counts per pixel in the myocardium divided by those in the mediastinum.\textsuperscript{22,23} The \textsuperscript{123}I-MIBG or \textsuperscript{123}I-BMIPP clearance from the myocardium was calculated as follows: (initial activity – delayed activity)/ initial activity × 100.

**Echocardiography**

*Echocardiographic recording:* The heart was imaged with an SSD-870, Aloka echocardiography by an experienced cardiologist. M-mode echocardiograms of the left ventricle from the parasternal long axis were recorded in the standard manner. Then the subjects were placed in the left lateral decubitus position. The transducer was oriented to obtain an apical four-chamber view that provided good visualization of the mitral anulus and leaflets. Doppler examination of mitral flow velocity was performed with the range-gated pulsed Doppler technique. The cursor line of the ultrasound beam was positioned as nearly parallel to the flow as possible. The Doppler sample volume was placed at the level of the mitral anulus.

**Echocardiographic measurements:** Left ventricular dimensions at end-diastole (LVEdD) and end-systole (LVESD) were measured in cm according to the American Society of Echocardiography criteria with an average of 3 to 5 cycles.\textsuperscript{24} The left ventricular shortening fraction (\%SF) was calculated as follows: (LVEdD – LVESD)/LVEdD × 100. Mitral peak flow velocities were measured in early diastole (peak E, in cm/second) and at the time of

### Table 1: Characteristics of anthracycline patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Cancer type</th>
<th>Drugs (total dose)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>f</td>
<td>55</td>
<td>AML</td>
<td>DNR 500 mg</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>44</td>
<td>AML</td>
<td>DNR 360 mg</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>23</td>
<td>ALL</td>
<td>DXR 250 mg</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>39</td>
<td>AML</td>
<td>DNR 360 mg, ACR 540 mg</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>46</td>
<td>AML</td>
<td>DNR 500 mg, ACR 220 mg</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>58</td>
<td>AML</td>
<td>ACR 1,260 mg</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>64</td>
<td>MM</td>
<td>DXR 96 mg</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>27</td>
<td>ML</td>
<td>DXR 350 mg</td>
</tr>
<tr>
<td>9</td>
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<tr>
<td>10</td>
<td>m</td>
<td>71</td>
<td>ML</td>
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<tr>
<td>11</td>
<td>f</td>
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<td>DXR 320 mg</td>
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<td>12</td>
<td>m</td>
<td>64</td>
<td>ML</td>
<td>DXR 240 mg</td>
</tr>
<tr>
<td>13</td>
<td>m</td>
<td>64</td>
<td>ML</td>
<td>DXR 380 mg</td>
</tr>
</tbody>
</table>

atrial systole (peak A). The ratio of peak mitral flow velocity in early diastole to mitral flow velocity at the time of atrial systole was calculated (E/A ratio).

**Statistics**

The data were reported as the mean ± one standard deviation. The differences in H/M ratio, clearance, LVEDd, LVESd, SF, peak E, peak A and E/A ratio were compared by a Student’s t-test. A value < 0.05 was considered significant.

**RESULTS**

**Case presentation**

Myocardial $^{123}$I-MIBG and $^{123}$I-BMIPP anterior images of a patient treated with doxorubicin are shown in Figure 1. In $^{123}$I-MIBG images, the left ventricular myocardium was not visible which indicated a marked decrease in cardiac $^{123}$I-MIBG uptake. However, in $^{123}$I-BMIPP images the myocardium was clearly visible, indicating a high left ventricular uptake of $^{123}$I-BMIPP.

**Scintigraphic results**

The heart-to-mediastinum ratio (H/M ratio) was compared between the patients treated with anthracycline and the control subjects (Table 2). A H/M ratio of $^{123}$I-MIBG was lower in patients treated with anthracycline than in control subjects (early: $1.5 ± 0.2$ vs. $1.9 ± 0.2$, $p < 0.01$, delay: $1.6 ± 0.3$ vs. $2.0 ± 0.3$, $p < 0.01$). The H/M ratio of $^{123}$I-BMIPP was similar between the two groups (early: $2.1 ± 0.2$ vs. $2.0 ± 0.2$, delay: $1.9 ± 0.3$ vs. $1.8 ± 0.2$).

$^{123}$I-MIBG and $^{123}$I-BMIPP clearance from the myocardium was compared between the anthracycline patients and the control subjects (Table 2). The clearance of $^{123}$I-MIBG ($27 ± 10\%$ vs. $22 ± 4\%$, $p < 0.05$), but not $^{123}$I-BMIPP ($24 ± 6\%$ vs. $26 ± 6\%$), was faster in patients treated with anthracycline than in the control subjects.

When the H/M ratio of $^{123}$I-MIBG smaller than mean – SD in the control subjects was considered abnormal, normal lower limits were 1.7 in both early and delayed $^{123}$I-MIBG images. Similarly, normal upper limit for $^{123}$I-MIBG clearance was determined as 26% from the values of control subjects (mean + SD). The sensitivities of $^{123}$I-MIBG imaging for the detection of anthracycline cardiotoxicity were 77% (10 of 13 patients) by the H/M ratio in the early image, 69% (9 of 13) by the H/M ratio in the delayed image and 54% (7 of 13) by the clearance.

**Table 2** Comparison of scintigraphic results

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 10)</th>
<th>Anthracyline (n = 13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{123}$I-MIBG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/M ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>early</td>
<td>$1.9 ± 0.2$</td>
<td>$1.5 ± 0.2$</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>delay</td>
<td>$2.0 ± 0.3$</td>
<td>$1.6 ± 0.3$</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>clearance</td>
<td>$22 ± 4%$</td>
<td>$27 ± 10%$</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>$^{123}$I-BMIPP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/M ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>early</td>
<td>$2.0 ± 0.2$</td>
<td>$2.1 ± 0.2$</td>
<td>ns</td>
</tr>
<tr>
<td>delay</td>
<td>$1.8 ± 0.2$</td>
<td>$1.9 ± 0.3$</td>
<td>ns</td>
</tr>
<tr>
<td>clearance</td>
<td>$26 ± 6%$</td>
<td>$24 ± 6%$</td>
<td>ns</td>
</tr>
</tbody>
</table>

H/M ratio: heart-to-mediastinum ratio

Vol. 8, No. 3, 1994
Table 3  Echocardiographic measurements

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Anthracycline</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDd (cm)</td>
<td>4.8 ± 0.4</td>
<td>5.0 ± 0.9</td>
<td>ns</td>
</tr>
<tr>
<td>LVEDs (cm)</td>
<td>3.0 ± 0.4</td>
<td>3.1 ± 0.6</td>
<td>ns</td>
</tr>
<tr>
<td>%SF (%)</td>
<td>36 ± 7</td>
<td>37 ± 8</td>
<td>ns</td>
</tr>
<tr>
<td>peak E (cm/sec)</td>
<td>66 ± 20</td>
<td>63 ± 22</td>
<td>ns</td>
</tr>
<tr>
<td>peak A (cm/sec)</td>
<td>43 ± 19</td>
<td>44 ± 24</td>
<td>ns</td>
</tr>
<tr>
<td>E/A</td>
<td>1.6 ± 0.3</td>
<td>1.4 ± 0.4</td>
<td>ns</td>
</tr>
</tbody>
</table>

LVEDd: left ventricular dimension at end-diastole, LVEDs: left ventricular dimension at end-systole, %SF: shortening fraction, peak E: peak mitral flow velocity in early diastole, peak A: peak mitral flow velocity in atrial systole, E/A: a ratio of peak E to peak A

Echocardiographic results

Echocardiographic measurements were compared between the patients treated with anthracycline and the control subjects (Table 3). The left ventricular end-diastolic dimension (LVEDd), left ventricular end-systolic dimension (LVEDs), left ventricular shortening fraction (%SF), mitral peak flow velocities at early diastole (peak E) and at atrial systole (peak A), and the ratio of peak E to peak A (E/A ratio) were comparable between the two groups.

DISCUSSION

The patients treated with anthracycline showed a lower uptake and faster clearance of 123I-MIBG in the myocardium than the control subjects, although echocardiographic measurements were similar. Myocardial 123I-BMIPP uptake and clearance were comparable between the two groups. The present findings suggest that myocardial imaging with 123I-MIBG may be useful in detecting myocardial damage in patients treated with anthracycline at the early stage when cardiac systolic and diastolic function is still preserved.

Numerous methods have been used for the detection of anthracycline-induced cardiotoxicity. Among them, serial radionuclide angiography is an effective and practical way for monitoring anthracycline-induced cardiotoxicity. However, the sensitivity of radionuclide-determined left ventricular ejection fraction (LVEF) at rest is relatively low, because local morphologic changes may precede a decrease in the LVEF. The contribution of exercise or pharmacologic stress testing remains still controversial, because an abnormal response in LVEF is nonspecific, and the stress test is often difficult to perform in patients with cancer. Diastolic dysfunction precedes the impairment of systolic function in patients receiving doxorubicin treatment. However, these changes in diastolic function are affected by several factors and are nonspecific.

Myocardial imaging with 99mTc-pyrophosphate and 11In-antimyosin was used to detect doxorubicin cardiotoxicity. Carrio et al. have recently reported that intense antimyosin uptake was observed in all patients at intermediate cumulative doses. Hiroe et al. have indicated in rats experiment that as the severity of morphological changes increases, there is an increase in myocardial antimyosin uptake. They also show a strong correlation between the antimyosin uptake and left ventricular end-diastolic pressure.

Metabolic abnormality may precede functional changes, but in the present study 123I-BMIPP was considered to be less useful in detecting anthracycline-induced myocardial damage. This is consistent with the experimental report that myocardial fatty acids uptake decreased only at high cumulative doses in adriamycin-induced cardiomyopathic rats. Fatty acid utilization could not be changed, because cumulative doses of anthracycline were relatively low in the present study. Further evaluation is required before the value of 123I-BMIPP imaging for the detection of anthracycline-induced myocardial damage can be accepted.

Recently, Wakasugi et al. have showed in a rat model of doxorubicin cardiomyopathy that 123I-MIBG accumulation in the myocardium decreases in an adriamycin dose-dependent manner. In the presence of normal LVEF and slight myocyte damage (scattered or focal vacuolar degeneration), 123I-MIBG uptake is significantly reduced. They suggest that MIBG may be a sensitive biochemical marker of adriamycin cardiomyopathy. However, the application of this isotope has not been tested in clinical trials. In the present study, we showed that patients treated with anthracycline, who had normal cardiac systolic and diastolic function, showed a lower uptake and faster clearance of 123I-MIBG in the myocardium than the control subjects.

Although tomographic images have advantages in assessing regional 123I-MIBG and 123I-BMIPP uptake, we used the anterior projection images. In 3 patients in whom the H/M ratio of 123I-MIBG was less than 1.3, tomographic images could not be reconstructed, because the count density was insufficient for image reconstruction. The heart-to-mediastinum ratio (H/M ratio) obtained from the anterior image was used to quantify cardiac 123I-MIBG uptake in the present study. It was reported that the H/M ratio of 123I-MIBG uptake was significantly related to the myocardial norepinephrine concentration and most potent to predict survival in patients with heart failure.

Mechanisms for the decreased uptake and faster clearance of 123I-MIBG in anthracycline-induced cardiomyopathy are still disputed. The following two mechanisms are the most relevant. The first is the disturbance of MIBG retention in the intracellular norepinephrine storage vesicles in patients treated with anthracycline. It was reported that the larger proportion of extra-vesicular 123I-MIBG in patients with dilated cardiomyopathy might account for more rapid washout of 123I-MIBG, because MIBG was more firmly bound inside norepinephrine storage vesicles than outside. The second is enhanced exocytotic release and turnover of MIBG due to systemic...

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adrenergic hyperactivity. There is an increase in plasma norepinephrine and a decrease in myocardial norepinephrine, reflecting systemic hyperactivity of the adrenergic nervous system, in adriamycin-induced cardiomyopathic rats. 16

Carrio et al. 31 have recently reported that patients with sarcomas treated with continuous infusion of adriamycin present with less antymusin uptake than those treated with a bolus injection, thus indicating less severe cardiotoxicity. Early detection of patients at risk for cardiotoxicity before cardiac function deteriorates has important clinical implications, since drug administration schedules can be individually changed to reduce the incidence and severity of heart failure. 31 Our results indicated that myocardial imaging with 123I-MIBG might detect patients at risk for anthracycline cardiotoxicity at an early stage when cardiac function was still preserved.

REFERENCES