Early Detection of Doxorubicin-Induced Myocardial Damage by Ultrasound Tissue Characterization With Integrated Backscatter

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Doxorubicin (DXR) is one of the most effective antineoplastic agents, but its use is limited by its myocardial toxicity. Myocardial injury reduces the cyclic variation of integrated backscatter (CV-IBS) and so the present study was designed to investigate whether CV-IBS can be used to detect the early phase of myocardial damage in patients receiving DXR. Thirty-four subjects constituted the study population, none of whom showed clinically evident heart failure. CV-IBS was obtained for both the interventricular septum and the left ventricular posterior wall in the parasternal short-axis view. Standard echographic measures of left ventricular function were also made. Subjects without DXR exposure or evident cardiac diseases served as controls. The total dose of DXR administered per patient was 339±164 mg/m² (range: 95–680 mg/m²). Conventional echographic parameters, including left ventricular wall thickness, dimensions, fractional shortening, and ejection fraction, showed no significant differences between the 2 groups. In contrast, CV-IBS was significantly decreased in the DXR group compared with the control group (septum: 4.7±1.7 vs 7.2±1.9 dB, p<0.0001; posterior wall: 6.7±2.2 vs 8.0±1.6 dB, p<0.05). CV-IBS can be used as an early indicator of DXR-induced myocardial damage in patients demonstrating normal left ventricular systolic function. (Circ J 2003; 67: 929–933)

Key Words: Doxorubicin; Integrated backscatter; Ultrasound tissue characterization

Doxorubicin hydrochloride (DXR) is one of the most effective antineoplastic agents for the treatment of a variety of malignancies, including lymphoma, leukemia, and solid tumors. However, the therapeutic benefit of this agent has been limited by its myocardial toxicity, which may result in congestive heart failure.1 DXR-induced myocardial damage is primarily related to the cumulative dose of the drug administered, which has prompted a general advisory to discontinue its use at a total dose of 550 mg/m² in an effort to reduce the incidence of heart failure.2–4 It is important to note, however, that marked variations in cardiotoxicity exist among patients receiving DXR, so routine compliance with the advisory may preclude the administration of DXR to a population of patients who might further benefit from its antitumor effect. Conversely, congestive heart failure may develop in a subset of patients receiving DXR with a cumulative dose <500 mg/m². In such cases, early detection of myocardial damage might enable implementation of preventive measures that could reduce the likelihood of congestive heart failure later in life.

Various techniques have been advocated for the detection of DXR-induced myocardial damage, including serial measurements of cardiac enzymes,5 electrocardiography,6 echocardiography,7–10 and radionuclide angiography.11,12 These techniques, however, focus predominantly on the evaluation of left ventricular contractile function and do not necessarily improve the sensitivity and/or specificity of detecting an early, subclinical stage of cardiac damage.

Ultrasound myocardial tissue characterization, based on the measurement of integrated backscatter, can provide quantitative information for characterizing the functional and structural state of cardiac muscle.13,14 Integrated backscatter demonstrates a cyclic variation throughout the cardiac cycle with the maximum value at end-diastole and the minimum at end-systole. The cyclic variation of integrated backscatter (CV-IBS) decreases with myocardial cell injury, a property that assists in detecting subclinical myocardial damage.15–20

In the current study, we measured the acoustic properties of the myocardium in patients with normal left ventricular systolic function who were receiving DXR to determine the feasibility of using CV-IBS for detecting an early phase of DXR-induced myocardial damage.

Methods

The investigation conformed to the principles outlined in the Declaration of Helsinki. The institutional ethics committee approved the study protocol and written informed consent was obtained from all patients prior to enrollment.

Study Subjects

Thirty-four patients constituted the study population, 17 of whom comprised the DXR-treatment group and the other 17 functioned as controls. Individuals within the DXR-treatment group were selected from the cohort of

(Received May 19, 2003; revised manuscript received August 27, 2003; accepted September 1, 2003)
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Circulation Journal Vol.67, November 2003
patients admitted to the hematology or orthopedic surgery departments at Teikyo University School of Medicine (9 male, 8 female; mean age 54±11 years).

Eligibility criteria included (1) history of DXR therapy for a malignant neoplasm, (2) no clinically apparent cardiac disease or dysfunction, and (3) left ventricular ejection fraction (LVEF) >50% by standard echocardiographic examination. Primary malignancies treated in these patients included lymphoma (n=7), multiple myeloma (n=6), osteogenic tumor (n=2), and acute leukemia (n=2). DXR was a component of combination therapy with other chemotherapeutic agents including cyclophosphamide (conventional dosages), and/or bleomycin, vincristine, cisplatin, or prednisone. None of the patients had received known cardiotoxic agents, or had undergone mediastinal or spinal irradiation. The control group included 17 patients admitted to hospital for echocardiographic examinations to evaluate heart murmurs or noncardiac chest pain (9 male, 8 female; mean age 49±8 years). Controls were required to have no clinical history of heart disease, pass a standard physical examination, and demonstrate normal systolic function on a standard echocardiographic examination.

**Echocardiographic Evaluation**

The echocardiographic examination consisted of a complete 2-dimensional (D), M-mode, and Doppler evaluation in combination with CV-IBS measurement using a SONOS 5500 (Philips Medical Systems, Andover, MA) equipped with a 2- to 4-MHz sector transducer. This system is capable of providing either conventional echographic images or 2-D integrated backscatter images in which the gray level is displayed proportional to the integrated backscatter amplitude.

Each patient rested in the left decubitus position and breathed in a relaxed manner. Standard 2-D and M-mode echographic examinations were performed from a parasternal view to evaluate left ventricular function, including left ventricular end-diastolic dimension, left ventricular end-systolic dimension, left ventricular fractional shortening, and LVEF.21 The Doppler echographic examination was also performed in an apical view to determine the ratio of early peak flow velocity to atrial peak flow velocity (E/A).22

**Integrated Backscatter Imaging**

Following standard echographic examinations, 2-D integrated backscatter images were depicted using echocardiographic software (Acoustic Densitometry, Philips Medical Systems) that quantifies the intensity of the backscattered echoes returning from myocardial cells within a user-defined region of interest (ROI). Details of the measurement procedure have been described previously.18,23 Briefly, following the acquisition of integrated backscatter images in the short-axis plane at the level of the papillary muscles, the sequential cine-loop images (2 s at 30 frames/s) were transferred to an optical disk. To obtain CV-IBS values for

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**Table 1 Clinical and 2-D and Doppler Echocardiographic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group (n=17)</th>
<th>DXR group (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49±8</td>
<td>54±11</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>9</td>
<td>9</td>
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<tr>
<td>Sinus rhythm</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>NYHA functional class I</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71.3±10.5</td>
<td>76.4±10.8</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>126±12</td>
<td>123±15</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74±9</td>
<td>73±9</td>
</tr>
<tr>
<td>LVEDd (mm)</td>
<td>45.2±4.3</td>
<td>46.2±5.0</td>
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<tr>
<td>LVDS (mm)</td>
<td>29.5±3.1</td>
<td>30.8±5.0</td>
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<tr>
<td>FS (%)</td>
<td>34.9±3.0</td>
<td>33.5±4.7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>62.5±5.6</td>
<td>60.1±4.6</td>
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<tr>
<td>End-diastolic IVS thickness (mm)</td>
<td>9.6±1.4</td>
<td>10.3±1.1</td>
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<tr>
<td>End-systolic IVS thickness (mm)</td>
<td>12.8±1.8</td>
<td>13.9±2.3</td>
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<tr>
<td>% Thickening of IVS</td>
<td>33.2±8.6</td>
<td>34.4±11.0</td>
</tr>
<tr>
<td>End-diastolic thickness of PW (mm)</td>
<td>9.5±1.2</td>
<td>9.9±1.1</td>
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<tr>
<td>End-systolic PW thickness (mm)</td>
<td>13.6±1.7</td>
<td>14.3±1.9</td>
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<tr>
<td>% Thickening of PW</td>
<td>44.9±14.7</td>
<td>43.6±9.2</td>
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<tr>
<td>Peak E wave velocity (cm/s)</td>
<td>68.1±14.4</td>
<td>63.6±14.3</td>
</tr>
<tr>
<td>Peak A wave velocity (cm/s)</td>
<td>63.3±11.7</td>
<td>74.9±15.0**</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.1±0.3</td>
<td>0.9±0.2*</td>
</tr>
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</table>

Values are expressed as mean±SD. *p<0.05, **p<0.01.

DXR, doxorubicin; NYHA, New York Heart Association; LVEDd, left ventricular dimension at end-diastole; LVDS, left ventricular dimension at end-systole; FS, fractional shortening; LVEF, left ventricular ejection fraction; IVS, interventricular septum; PW, posterior wall; E/A, peak E wave velocity/peak A wave velocity.
each site, we placed a ROI at the center of the septal wall and at the center of the posterior wall in each patient. The location of the ROI was manually adjusted on a frame-by-frame basis to keep this reference point within the myocardial midwall throughout each cardiac cycle. The power of the integrated backscatter signal contained within the ROI was determined in dB and a curve of integrated backscatter versus time was reconstructed. We defined the magnitude of CV-IBS as the difference between the minimum and maximum values within a cardiac cycle averaged over 2 or more consecutive cycles (Fig 1). The transmit power, compression setting, and time–gain compensation were kept constant at each integrated backscatter examination.

**Statistical Analysis**

Data is presented as mean±standard deviation. Statistical analyses were performed using Mann-Whitney U test for comparisons between 2 means and a linear regression test to compare E/A ratio and CV-IBS. Differences were considered significant at p<0.05.

**Results**

**Study Population**

The clinical characteristics and conventional echocardiographic variables of the 17 DXR-treated patients and 17 controls are listed in Table 1. None of these subjects demonstrated cardiovascular symptoms on entry to the study. In the DXR-group, the echocardiographic examination was performed at a mean interval of 440±525 days (range: 9–1,690 days) after initiation of DXR-treatment, and this timing was also at 118±151 days (range: 9–525 days) after completion of the DXR-treatment protocol used in the hospital. The cumulative dose of DXR administered per patient was 339±164 mg/m² (range: 95–680 mg/m²).

**Echocardiographic and Integrated Backscatter Measurements**

In neither the DXR nor the control group did the conventional 2-D echocardiographic examination reveal regional wall motion abnormalities, evidence of structural cardiovascular malformations, ischemic heart disease, or cardiomyopathy. The M-mode echocardiographic parameters, including left ventricular wall thickness, dimensions, fractional shortening, and LVEF, showed no significant difference between the DXR and control groups. However, the Doppler echocardiographic examination disclosed an increased peak atrial wave velocity (74.9±15.0 vs 63.3±11.7 cm/s, p<0.01) and a decreased E/A ratio in the DXR group compared with the controls (0.9±0.2 vs 1.1±0.3, p<0.05) (Table 1).

Ultrasound tissue characterization using integrated backscatter revealed that the CV-IBS in the septum of the DXR group was significantly decreased compared with that of the control group (4.7±1.7 vs 7.2±1.9 dB, p<0.0001). A similar relationship between the DXR and control groups was observed in the CV-IBS of the posterior wall (6.7±2.2 vs 8.0±1.6 dB, p<0.05) (Fig 2). No significant relationships were observed between cyclic variations of integrated backscatter (CV-IBS) and peak early wave velocity/peak atrial wave velocity (E/A) ratio in either (A) the septal wall or (B) the posterior wall.

**Discussion**

Despite its dose-dependent cardiotoxic effects, DXR remains in use because of its efficacy in the treatment of several types of malignant tumors. At present, conventional
echocardiography and radionuclear imaging modalities, which primarily assess the systolic properties of the left ventricle, are the most commonly used methods to evaluate cardiac function during DXR treatment. In the current study, we demonstrated that the peak E/A ratio and CV-IBS were decreased in patients receiving DXR treatment despite the conventional 2-D and M-mode echocardiographic parameters indicating preservation of systolic cardiac function. With regard to the decreased E/A ratio, our results are consistent with the findings of Marchandise et al, which suggested that diastolic dysfunction precedes systolic dysfunction in the evolution of DXR-induced myocardial damage.1 It is thus anticipated that conventional measures of left ventricular function, which focus on the systolic function, have significant limitations in identifying patients most likely to develop late cardiac failure.

CV-IBS was also altered in patients treated with DXR, despite preservation of systolic function. The mechanism responsible for reduced CV-IBS in the DXR-treatment group remains unknown. Although previous studies have suggested that the magnitude of CV-IBS is dependent upon left ventricular contractility,24–26 this is contradicted by the fact that our subjects showed normal systolic function. Decreased CV-IBS appears unrelated to diastolic dysfunction as well, because the linear regression test revealed no statistically significant relationship between the CV-IBS and the E/A ratio in either group. Thus, possible explanations for the reduced CV-IBS in DXR-treated patients may reflect a pathologic, rather than functional, alteration of the myocardium. In fact, Vered et al have suggested that myocardial fibrosis is an additional determinant of CV-IBS in patients with idiopathic dilated cardiomyopathy.27 It has also been suggested that integrated backscatter is directly related to sarcomere length and myocardial thickness; and that changes in their size during the cardiac cycle may be responsible for the CV-IBS.28 Similar pathologic changes may have contributed to the reduction in CV-IBS in our patient population.

In the patients treated with DXR, the reduction in CV-IBS of the septum was more prominent than that of the posterior wall. Although the mechanisms for this observation were not clear in the current study, it is possible that histologic changes of the left ventricles may occur heterogeneously. Further study is needed to confirm this hypothesis.

Finally, in contrast to the E/A ratio, which has been shown to be influenced by several clinical factors including sex, age, heart rate, and most importantly ventricular loading condition, CV-IBS is less influenced by these factors.29,30 In this regard, CV-IBS may have an advantage over E/A ratio as an indicator of DXR-induced myocardial damage. Whether Doppler measurement of diastolic filling patterns or tissue characterization by CV-IBS is superior in detecting DXR-induced myocardial damage remains undetermined.

Study Limitations

The number of patients included in this study was small and so a larger study is required to validate the results of the current study. We included patients who were taking a small dose of DXR. Although DXR-induced myocardial damage is thought to develop at the range <100 mg/m², there remains the possibility that some of the present patients did not have myocardial damage because of variations in their tolerance.31 The prognostic significance of subclinical myocardial damage detected by CV-IBS is unknown. An intriguing question is whether the evaluation of CV-IBS in patients with malignant neoplasms may alter the therapeutic strategy, including changes in agents and/or timing of chemotherapy. Modifications in the treatment approach pertaining to the timing of and dose of DXR, or its use in combination with other chemotherapeutic agents, should be correlated with longitudinal echocardiographic measures of ventricular function supplemented by CV-IBS.

References


Circulation Journal Vol.67, November 2003


