Doxorubicin Cardiotoxicity: Response of Left Ventricular Ejection Fraction to Exercise and Incidence of Regional Wall Motion Abnormalities*

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国문초록

Doxorubicin의 심독성에 관한 연구

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哀 錦 華

Doxorubicin은 최근 가장 광범위하게 사용되고 있는 항암제중의 하나이며 그 특이한 효과를 인정받고 있으나 치료중에 부작용으로 나타나는 부작용 때문에 사용이 제한되어 왔다. 부작용 중에서도 특히 심독성은 양상이 특이하고 심한 경우 심근경색으로 인한 사망도 발생할 수 있어 이를 조기에 발견하여 심독성을 예방하는 것이 매우 중요한 일이다. 본 연구는 Doxorubicin으로 치료하고 있는 53명의 각종 암환자들을 대상으로 방사성을 동위원소를 이용하여 좌심실 기능 검사를 실시하여 투약으로 인한 심독성의 유무를 관찰하고 특성을 관찰하였다. 또한 Doxorubicin투여 총량과 심독성과의 관계 및 운동부하검사에 대한 반응을 보기 위해서 Multiple ECG Gated Blood Pool Scan(MUGA)을 실시하여 다음과 같은 결과를 얻었다.

대상환자 53명중 제 1군은 14명으로 투약전 및 투약후 검사를 실시하였으며 제 2군 22명은 투약 중 2~3회 검사를 실시하였으며 나머지 17명은 투약중 1회 실시하였다. 모든 환자에서 안정시 좌심

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SUMMARY

Radionuclide multiple ECG gated equilibrium blood pool images of the heart were performed to evaluate cardiac function of 53 patients who received doxorubicin (mean dose: 428 mg/m² BSA) treatment of various malignancies. Fourteen patients (Group I) received pre-treatment (baseline) studies: they demonstrate a significant decrease of resting LVEF after therapy (p<0.01). Twenty—two patients (Group II) had serial studies during treatment, also with a significant fall of resting LVEF (p<0.001). Eighteen patients in Groups I and II had supine exercise studies and the exercise response of LVEF did not deteriorate after treatment. We found regional wall motion abnormalities (mild apical hypokinesis) at rest by visual inspection in 33 out of 36 Group I and Group II patients (91.7%) who received doxorubicin.

In the baseline or initial study, only 4 of these 36 patients demonstrated WMA. In patients with exercise studies, WMA occurred in 22 out of 30 at rest (73%) but only 14 out of 30 (47%). 7 out of 18 (37%) in Groups I and II during exercise confirmed by phase analysis.

The results indicate that resting LVEF declines after doxorubicin treatment but that the response to exercise is unaffected. Exercise radionuclide angiographically does not improve upon study at rest for the detection of doxorubicin relatively high incidence, more readily detectable at rest. However, the exercise study can distinguish doxorubicin related WMA from those due to coronary artery disease.

INTRODUCTION

Doxorubicin is one of the most effective chemotherapeutic agents presently available for the malignant neoplastic disease (1—7). Unfortunately, cardiotoxicity is a well recognized effect of this agent and is frequently a dose—limiting factor in its administration (8—13).

Doxorubicin cardiotoxicity is characterized by acute effects—mainly transient benign arrhythmias (14, 15) and by chronic development of dilated cardiomyopathy (8—13, 16, 17).

The cardiotoxicity is generally thought to correlate with cumulative doses (2—14) but there is considerable variation in the patient’s susceptibility to the doxorubicin effect on the myocardium (3, 6, 9, 18—24).

Various methods for evaluating the cardiotoxic effect have been employed such as ECG (9, 25—27), systolic time interval (28—30), echocardiography (31—33), radionuclide angiocardiology (14, 18, 19, 22, 34—36), cardiac catheterization and endomyocardial biopsy (4,
23, 29, 37). Although endomyocardial biopsy has been used to monitor the patients receiving doxorubicin treatment, the morphologic monitoring of patients is of limited value for predicting the development of doxorubicin cardiotoxicity (4, 38). In contrast, the physiologic evaluation of left ventricular function may improve the sensitivity of monitoring patients for clinical evidence of latent cardiotoxicity (19, 23, 36). Noninvasive methods such as ECG, systolic time interval and echocardiography have proved to be unreliable tests for detecting latent cardiotoxicity (9, 18, 19), but radionuclide angiography is an accurate, sensitive, and reproducible means for evaluating cardiac function and its functional reserve.

Previous studies revealed a decline in resting left ventricular ejection fraction (2-4, 6-11, 14-23) and some studies suggested that an exercise test increases the sensitivity of early detection of doxorubicin cardiotoxicity (16, 19, 23, 28).

The purpose of this study was to evaluate the effects of doxorubicin on rest and exercise left ventricular function in order to define the diagnostic benefit of exercise testing in comparison to the serial evaluation of resting function. Additionally, we investigated the incidence of regional wall motion abnormalities in doxorubicin treated patients, its relationship to the dose administered and its response to exercise.

METHODS

Study population

The study population consisted of 53 patients (25 males, 28 females) 18 to 76 years of age with an average of 51 years. A mean dose of doxorubicin 428.8±126.00mg/m² BSA was administered in these patients for the treatment of neoplastic diseases at the time of the study. The composition of primary diseases in the patients is shown in Table 1.

Care was taken to exclude patients with evidence of coronary artery disease and/or valvular heart disease by history, physical examination and ECG criteria.

Of the 53 patients, 36 had multiple radio- nuclide studies and were divided into two groups. In Group I, a baseline study was done before doxorubicin treatment was begun and repeated two months after the last dose of doxorubicin in 14 patients. The mean interval between the two studies was 6±3.2 months. Among them, 7 patients had an exercise test. In Group II, serial studies were performed during doxorubicin treatment in 22 patients and among them, 11 patients had an exercise test; the mean interval between both studies was 7±3.3 months.

Radionuclide Technique

For multiple ECG gated equilibrium blood pool imaging of the heart, 20 mCi of technetium-99m pertechnetate in vitro labeled autologous red blood cells were injected intravenously. Imaging was performed with a standard gamma camera (Series 420 Mobile Gamma, Technicare) equipped with a high-resolution low-energy parallel hole collimator described previously (39). In brief, the detector was tilted 10 to 15 degrees caudally and the left anterior oblique (LAO) projection was adjusted until left ventricle and right ventr-
icle were optimally separated on the persistence oscilloscope. The image data were acquired with a dedicated nuclear medicine minicomputer (VIP 550, Technicare) and formatted into a 64 by 64 matrix. Data were recorded for 4 minutes at rest and for 3 minutes during exercise.

The left ventricular ejection fraction (LVEF) was calculated from the LV time activity curve constructed from the 16 sequential equilibrium cardiac blood pool images. A "variable" region of interest was assigned manually to the LV on each of the 16 frames and EF was calculated from the time activity (volume) curve from the difference between maximum and minimum counts divided by the maximum counts (41).

The regional wall motion abnormalities (WMA) were assessed subjectively by two experienced observers. The findings were defined as hypokinesis, akinesis and dyskinesis as described earlier (39, 40).

**Exercise Protocol**

Supine exercise was performed using a bicycle ergometer (Collins pedal mode) as described previously (39, 40). After the resting study, bicycle exercise was begun at a workload of 25 watts and was increased every 4 minutes in 25 watt increments. Images were acquired during the final 3 minutes at each workload. Exercise was continued until shortness of breath, fatigue and chest pain occurred. Blood pressure (measured by a standard cuff sphygmomanometer) and heart rate (determined from the ECG) were recorded during the final minutes at each workload.

**Phase Analysis of Equilibrium Blood Pool Images**

The phase analysis of images were performed as described previously (39, 41). We used the discrete Fourier transform. The amplitude image is used to create a mask over the phase image. Only those pixels with an amplitude above a certain manually selected threshold (usually 10% of the maximum amplitude) are displayed and counted so that the pixels outside the heart do not contribute to the phase distribution histogram. From the masked phase image, a histogram of the phase distribution from 0 to 360 degrees on the abscissa and the number of pixels within each 9 degree range on the ordinate is generated. The LV is manually outlined on the enddiastolic frame and a second histogram of the phase distribution is plotted and automatically analyzed. The mean phase of the ventricular peak is measured as well as the standard deviation from the mean of the peak (SDP). The SDP describes the width of the peak and is used as an index of synchronicity of LV wall motion. An SDP of 12° was defined as the upper normal limit by a study in normal volunteers (39). On the phase image, the localization of any segment with an out-of-phase wall motion as well as any changes in phase distribution from rest to exercise are noted and compared to the visually assessed wall motion abnormalities.

**Statistical Analysis**

Student’s t—test for paired and unpaired data is employed to evaluate inter—group difference for statistical significance. All mean values are given with one standard deviation (SD) and comparisons with p < 0.05 were considered statistically significant.

**RESULTS**

**LVEF At Rest and During Exercise**

For the 53 patients undergoing doxorubicin treatment, the resting LVEF vs. dose is shown in Figure 1. The linear correlation coefficient r = 0.026 demonstrates lack of significance. The mean dose is 428.8 mg/m² (σ = 126.0); the mean LVEF is 47.0% (σ = 6.6).

For 27 patients receiving less than (more than or equal to) 450 mg/m², LVEF is 48.6% (σ = 6.0) [45.3% (σ = 6.1)], p < 0.10. Among
Fig. 1. Rest LVEF and cumulative doxorubicin dose in all 53 patients.

Fig. 2. LVEF response to exercise in 30 patients.
the 30 exercised patients, 16[14] receiving less than [more than or equal to] 450 mg/m², the exercise LVEF is 52.1% (± 5.9%) [47.3% (± 11.3%)], p < 0.20.

Sixteen of the thirty exercised patients had an increase of LVEF of greater or equal to 5% with exercise. None of 14 patients receiving less than 450 mg/m² had a normal exercise LVEF response; seven of 16 receiving more than or equal to 450 mg/m² had a normal response (Figure 2).

**Group I: With Baseline Studies**

In the 14 Group I patients who were studied before and after doxorubicin treatment (Figure 3), the resting LVEF before treatment was 54.6±4.9% and decreased significantly to 45.4±6.2% after treatment (p < 0.001).

In 7 patients in this group, the rest and exercise LVEF before and after treatment of doxorubicin was determined. Six of 7 patients increased the LVEF more than or equal to 5% during the base line exercise test, while 5 of 7 increased more than or equal to 5% during the second test. The heart rate response and maximum work load were not significantly different for both exercise tests.

The resting LVEF before doxorubicin treatment was 52.9% (± 5.0%) and increased significantly to 62.7% (± 6.8%) with exercise (p < 0.05); the resting LVEF after doxorubicin treatment was 45.9% (± 6.6%) and increased significantly to 51.4% (± 7.7%) with exercise (p < 0.01). There were not significant differences in heart rate response and workload between the pretreatment and post – treatment patients.

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Fig. 3. Rest and exercise LVEF in 14 Group I patients before and after doxorubicin treatment.
Group II: With Serial Studies

In the 22 Group II patients, serial studies during treatment with doxorubicin were performed (Figure 4). The resting LVEF of initial studies was 53.1 ± 6.2% and decreased significantly to 46.9 ± 5.9% in follow-up studies (p < 0.001).

Regional Wall Motion Abnormalities

In the majority of our patients on doxorubicin treatment, we found regional wall motion abnormalities by visual inspection which was characterized in all cases by a apical hypokinesis. The WMA occurred in 68% of the entire 53 patients studied at rest (Table II). The incidence of WMA was 55%, 16 of the 27 patients who received less than 450 mg/m² of doxorubicin, but 83%, 20 of the 24 patients who received more than or equal 450 mg/m² of doxorubicin. The WMA in 30 patients with an exercise test occurred in 73.3% (22) at rest and in 47% (14) during exercise. In the 14 patients who received less than 450 mg/m² of doxorubicin, the WMA occurred in 57.1% (8) at rest and in 21.4% (3) during exercise. In the 16 patients who received more than 450 mg/m² of doxorubicin, the WMA occurred in 87.5% (14) at rest and in 68.8% (11) during exercise.

No WMA at rest was observed in the 14 Group I patients before doxorubicin treatment, but the WMA at rest occurred in 93% (13) after doxorubicin treatment. In 7 patients with an exercise test, none had the WMA at rest before doxorubicin treatment but the WMA occurred in 100% at rest and in 28% (2) during exercise after doxorubicin treatment. The WMA at rest in 22 Group II patients occurred in 19% (4) in the initial studies and 90% (2) in the
Table 2. Incidence of regional wall motion abnormalities at rest and with exercise in patients on doxorubicin

<table>
<thead>
<tr>
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<th>Total</th>
<th>Doxorubicin dose (mg/m²)</th>
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<tr>
<td></td>
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<tr>
<td>53 Patients at rest</td>
<td>36/53 (67.9%)</td>
<td>16/27 (55.2%)</td>
<td>20/26 (83.3%)</td>
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<td>at rest</td>
<td>22/30 (73.3%)</td>
<td>8/14 (57.1%)</td>
<td>14/16 (87.5%)</td>
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<td>with exercise</td>
<td>14/30 (46.7%)</td>
<td>3/14 (21.4%)</td>
<td>11/16 (68.8%)</td>
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Group I: After treatment

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<td>7 Patients with exercise</td>
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<tr>
<td>at rest</td>
<td>7/7 (100)</td>
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<td>with exercise</td>
<td>2/7 (28.6)</td>
<td>1/2 (50.0)</td>
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Group II:

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<td>Follow-up studies</td>
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<td>11/12 (91.7)</td>
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11 Patients with exercise

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<td>Initial studies at rest</td>
<td>3/8 (27.3)</td>
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<td>Follow-up studies at rest</td>
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<td>3/3 (100)</td>
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<td>5/11 (45.4)</td>
<td>1/3 (33.3)</td>
<td>4/8 (50.0)</td>
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follow-up studies. The WMA in 11 Group II patients with an exercise test occurred in 27% (3) at initial studies and in 100% at rest and in 45% (5) during exercise at follow-up studies.

Phase Analysis

Phase analysis of images were performed for Group I and II patients to confirm the WMA described visually.

In Group I (Figure 5), the SDP of LV at rest before treatment in 14 patients was 9.6 ± 1.7 degrees and increased significantly to 12.8 ± 3.0 degrees after doxorubicin treatment (p < 0.001). In 6 patients receiving less than 450 mg/m² of doxorubicin, the SDP of LV at rest was 10.1 ± 2.0 degrees before treatment and 13.5 ± 3.2 degrees after treatment (p < 0.05). In 8 patients receiving more than 450 mg/m² of doxorubicin, the SDP of LV at rest was 9.1 ±
1.5 degrees before treatment and 12.3 ± 3.0 degrees after treatment (p < 0.01). In 7 patients with exercise after doxorubicin treatment, the SDP of LV was 11.2 ± 1.8 degrees at rest and 9.6 ± 1.9 degrees during exercise (p < 0.025) shown in Figure 6.

In Group II (Figure 7), the SDP of LV at rest on initial studies of 22 patients was 10.4 ± 1.9 degrees and increased significantly to 12.5 ± 3.1 degrees on follow-up studies during doxorubicin treatment (p < 0.005). In 9 patients in this group who received less than 450 mg/m² of doxorubicin, the SDP of LV at rest was 10.4 ± 1.6 degrees on initial studies and 12.9 ± 3.7 degrees on follow-up studies (p < 0.05). In 13 patients who received more than 450 mg/m² of doxorubicin, the SDP of LV at rest was 10.4 ± 2.2 degrees on initial studies and 12.2 ± 2.6 degrees on follow-up studies (p < 0.05). In patients with exercise on the follow-up studies, the SDP of LV was 11.1 ± 1.6 degrees at rest and 9.8 ± 1.9 degrees during exercise as shown in Figure 8 (p < 0.20).

**DISCUSSION**

The results of this study confirm earlier reports on the cardiotoxic effects of doxorubicin and its relationship to the cumulative dose of the drug (2–14). The mean ejection frac-
on fraction in the group receiving more than 450 mg/m² was significantly lower than in the group receiving less than 450 mg/m². However, the individual variation in ejection fraction and in drug effect precludes a significant linear correlation between dose and EF impairment. The left ventricular ejection fraction used in this study as well as in previous investigations as parameters of left ventricular function does not directly reflect cardiac contractility but the combined effect of preload, afterload and contractility on left ventricular fiber shortening. Since no other hemodynamic measurements besides ejection fraction were made in this study, part of the observed interindividual variation of the drug effect may be explained by the choice of this parameter for LV function.

In our patient population, 33 out of 53 patients had an abnormal ejection fraction after treatment. The incidence of an abnormal ejection fraction was slightly higher (19/26) in the patients receiving more than or equal to 450 mg/m² as compared to the patient receiving less than 450 mg/m² (14/27). The data however show that 20/53 patients had a normal ejection fraction and that some patients maintained a normal LVEF even after exposure to a large dose of doxorubicin indicating a large interindividual variation in the susceptibility to the cardiotoxic effect of doxorubicin.

In earlier reports it has been stated that exercise imaging increases the sensitivity of early detection of doxorubicin induced cardiomyopathy (16, 19, 23, 38). The failure to increase ejection fraction during exercise is commonly thought to be a sensitive sign of ventricular dysfunction, most widely used as diagnostic criteria in patients suspected of coronary artery disease (43-45). An abnormal exercise response however is not specific for any cardiac disease and has even been found in a considerable number of normal female subjects (46). Since patients on doxorubicin treatment represent generally a mixed population with unknown prevalence of asymptomatic coronary artery disease, an abnormal exercise response, especially in the older age group, may not be specific for doxorubicin induced cardiomyopathy. We attempted in our study population to carefully exclude the patients with clinical evidence of coronary artery disease, but only a few patients had proven normal coronary arteries by angiography. Additionally, patients treated for neoplastic diseases often have limited exercise tolerance because of their primary disease which further limits the diagnostic value of the exercise test. The data on heart rate response and the mean work load in our patients indicate that the exercise level was submaximal in most cases. It has been shown previously that the less than maximal exercise level decreased the sensitivity and specificity of the test for detecting an abnormal ventricular function.

In 30 patients exercised undergoing treatment with doxorubicin, 14 had an abnormal exercise response defined as the failure to increase LVEF by at least 5%. However, only three of these had a normal resting LVEF (50%). Thus, for this group of patients, exercise is of low yield for detecting abnormal LV function. Further, an abnormal exercise response is well known to be quite non-specific. In fact, we showed above that the mean exercise response is unchanged for the patients in Group I and II. Exercise thus does not help us detect doxorubicin cardiotoxicity.

In serial studies at rest, the effect of doxorubicin of LV function can be better characterized since rapid development of coronary artery disease in a few months occurs rarely and changes of cardiac performance more likely reflect the effect of the therapeutic intervention. In the Group I patients studied before and after doxorubicin, a new abnormal exercise response was present in only 1 of 7 patients. However, the resting ejection fraction decreased in 12 of 14 patients when the base-
line value was compared with the post-treatment value. These data suggest that the change in resting function is more sensitive than the exercise response to detect the toxic effects of doxorubicin. The same trend could be demonstrated in Group II patients with serial studies during treatment in which 6 of 11 patients maintained a normal exercise response while 17/22 demonstrated a decrease in resting function. Therefore, we think that serial determination of resting ejection fraction in patients receiving doxorubicin is sensitive for the evaluation of the cardiotoxic effect. Exercise testing may increase the sensitivity for detection of abnormal LV function in a single study, but does not affect the sensitivity in serial studies and, therefore, is only of limited value. It may actually help rule out acutely developing coronary artery disease.

Regional left ventricular wall motion abnormalities are a well known finding in patients with coronary artery disease but have also been described in patients with other cardiac disease as valvular heart disease and cardiomyopathies (39, 47–50). Regional impairment of wall motion has to our best knowledge not been reported in patients receiving doxorubicin treatment. The relatively high incidence (68 % at rest in 53 patients) makes undetected coronary artery disease as etiologic factor very unlikely. Secondly, the incidence of regional wall motion abnormalities decreased during exercise, again a finding which is not consistent with ischemic heart disease. The occurrence of wall motion abnormalities was higher in patients who received more than 450 mg/m² of doxorubicin and hence paralleled the impairment of global left ventricular function. This dose dependence is further substantiated by the fact that the incidence of wall motion abnormalities increased in patients with serial studies during treatment. In all cases the wall motion abnormality involved the apex of the ventricle, a segment which is also affected in patients with valvular heart disease (39, 49, 50).

The morphologic findings of doxorubicin cardiomyopathy are similar to these found in dilated cardiomyopathy and may represent diffuse myocardial involvement rather than a focal lesion (3, 7, 23, 29, 37). Therefore, we hypothesize that the regional impairment described above reflects a functional abnormality caused by change of left ventricular geometry. Since doxorubicin may affect the structural tissue of the heart, regional changes in loading conditions could lead to a regional decrease of myocardial fiber shortening. During exercise and the concomitant increase of adrenergic stimulation, these regional differences in loading conditions may be overridden and therefore explain the observation of the decreased incidence of regional wall motion abnormalities during exercise.

Phase analysis is a more objective way to evaluate synchrony of the left ventricular contraction pattern and has been used to quantitate the temporal sequence of regional wall motion (39, 41, 42). The measurements of the standard deviation of the left ventricular phase distribution (SDP) in our study confirms the visual impression. We did find an increase of SDP in serial studies paralleling the increased incidence of visually observed wall motion abnormalities. The SDP decreased during exercise, again compatible with the visually obtained improvement of wall motion abnormalities. In contrast, it has been shown that in patients with coronary artery disease and exercise induced ischemia, SDP increased markedly during exercise (39). The discrepancy between our findings and an ischemic phase pattern furthermore supports that the observed wall motion abnormalities are due to the toxic effect of doxorubicin and not a consequence of coronary artery disease.

**CONCLUSION**

We conclude from this study that the cardio-
toxic effect of doxorubicin can be monitored by serial resting ventricular function studies. Exercise testing may increase the sensitivity of detection of ventricular dysfunction if only one study during treatment is done, but the known low specificity of the ventricular exercise response offsets the diagnostic gain. Regional wall motion abnormalities occur with a relatively high incidence in patients undergoing doxorubicin treatment and are more often detectable at resting conditions. In fact, they frequently disappear with exercise. Phase analysis allows objective assessment of synchrony of left ventricular wall motion in patients treated with doxorubicin and supports the visual observation of wall motion abnormalities.

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