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Doxorubicin cardiotoxicity: Response of left ventricular ejection fraction to exercise and incidence of regional wall motion abnormalities

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Summary

Gated radionuclide ventriculograms were performed to evaluate cardiac function in 53 patients who received doxorubicin treatment for various malignancies (mean dose: 449 ± 128 mg/m² BSA). In fourteen patients (Group I) function was evaluated before and after treatment; there was a significant decrease of resting left ventricular ejection fraction after therapy ($p<0.001$). Twenty-two patients (Group II) had serial studies during treatment which also showed a significant fall of resting left ventricular ejection fraction ($p<0.001$). Eighteen patients in Groups I and II had supine exercise studies. A normal exercise response was maintained in the majority of patients. Exercise testing added little to the diagnostic performance when compared to serial resting studies. We found regional wall motion abnormalities (mild apical hypokinesis) at rest by visual inspection in 33 of 36 Group I and Group II patients who had received doxorubicin. In the baseline or initial study, only 4 of these patients demonstrated WMA. In 18 Group I and II patients who were exercised, 3 had wall motion abnormalities during the initial study. All of these patients demonstrated wall motion abnormalities at rest after the second study, however only 7 of 18 demonstrated abnormalities during the exercise study.

The results indicate that resting left ventricular ejection fraction declines after doxorubicin treatment. Exercise radionuclide angiography may not increase diagnostic accuracy for the detection of doxorubicin related cardiotoxicity. Regional wall motion abnormalities occur with a relatively high incidence following doxorubicin therapy, more readily detectable at rest. However, the exercise study can distinguish doxorubicin related wall motion abnormalities from those due to coronary artery disease.

Introduction

Doxorubicin is an effective chemotherapeutic agent for the treatment of malignant neoplastic disease [1–7]. Unfortunately, the amount of doxorubicin that can be administered is limited by its well known cardiotoxicity [8–13]. Toxic effects occur acutely, mainly in form of transient benign arrhythmias [14, 15] and chronically, by development of dilated cardiomyopathy [8–13, 16, 17]. The degree of cardiotoxicity is generally thought to be a function of the cumulative dose [2–14]. However, the susceptibility to the toxic effects of doxorubicin varies considerably between patients [3, 6, 9, 18–24].

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Cardiotoxicity has been observed with several methods such as ECG [9, 25–27], systolic time intervals [28–30], echocardiography [31–33], radionuclide ventriculography [14, 18, 19, 22, 34–36], cardiac catheterization and endomyocardial biopsy [4, 23, 29, 37]. However, morphologic monitoring by endomyocardial biopsy is of limited value in predicting development of cardiotoxicity [4, 38]. In contrast, monitoring cardiac function may be more sensitive for detecting early cardiotoxicity [19, 23, 36]. Radionuclide ventriculography is an accurate 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]. Several studies also suggested that an exercise test increases the sensitivity of early detection of doxorubicin cardiotoxicity [16, 19, 23, 38].

The purpose of this study was to evaluate the effects of doxorubicin on left ventricular function at rest and exercise in order to define the diagnostic benefit of exercise testing in comparison to 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 449.3 ± 128 mg/m^2 BSA was administered in these patients for treatment of neoplastic diseases at the time of the study. 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 radionuclide studies and were divided into two groups. In 14 Group I patients, a baseline study was done prior to doxorubicin treatment and repeated two months after the last dose of doxorubicin. 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

Data acquisition

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 Camera, Technicare) equipped with a high-resolution, low-energy, parallel hole collimator [39]. In brief, the detector was tilted 10 to 15 degrees caudally and the left anterior oblique (LAO) projection was adjusted until the left and right ventricle were optimally separated on the persistence scope. 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.

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 at each workload. Exercise was continued until shortness of breath, and/or fatigue occurred. Blood pressure and heart rate were recorded during the final minutes at each workload.

Data processing

The left ventricular ejection fraction was calculated from the left ventricular 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 ejection fraction was calculated from the time activity (volume) curve as the difference

between maximum and minimum counts, divided by the maximum counts [41].

Regional wall motion abnormalities were assessed visually by two experienced observers. The findings were defined as hypokinesis, akinesis, and dyskinesis, as described earlier [39, 40].

Additionally, synchronicity of regional wall motion was assessed by phase analysis. The phase analysis of images was performed as described previously [39, 41]. Using 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 left ventricle is manually outlined on the end-diastolic 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. The standard deviation of the peak describes the width of the peak and is used as an index of synchronicity of LV wall motion. A standard deviation of 12° was defined as the upper limit of normal in a study in normal volunteers. On the phase image, the localization of any segment with 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 differences for statistical significance. All mean values are given with one standard deviation (SD) and comparisons with $p<0.05$ were considered statistically significant.

Results

Left ventricular function at rest and during exercise

The relationship of left ventricular function, expressed as global left ventricular ejection fraction, and the amount of doxorubicin received in the cohort of 53 patients is displayed in Fig. 1. There was no linear correlation found ($r = 0.026$ N.S.). The mean left ventricular ejection fraction was $47.0 \pm 6.6\%$, the mean dose of doxorubicin 449 ± 128 mg/m^2 BSA. For 29 patients receiving less than 450 mg/m^2 doxorubicin, the ejection fraction averaged $48.6 \pm 6.0\%$, while in the 24 patients with more than 450 mg/m^2, the mean ejection fraction was $45.3 \pm 6.1\%$ ($p<0.05$).

Fig. 2 summarizes the results obtained at rest and during exercise in 30 patients. In 15 patients receiving less than 450 mg/m^2 doxorubicin, the ejection fraction increased to $52.1 \pm 5.9\%$. In 15 patients with a dose of more than 450 mg%, the exercise ejection fraction during exercise was not significantly different from baseline value. Nine of the 15 patients receiving less than 450 mg/m^2 had a normal exercise left ventricular ejection fraction response of more than 5% increase, while only 7 of 16 with more than 450 mg/m^2 demonstrated an increase of more than 5% (n.s).

Group I: Patients studied before and after treatment

In the 14 Group I patients who were studied before and after doxorubicin treatment (Fig. 3), the resting LVEF before treatment was $54.6 \pm 4.9\%$ and decreased significantly to $45.4 \pm 6.2\%$ after treatment ($p<0.001$). In 7 patients in this group, the rest and exercise left ventricular ejection fraction before and after treatment of doxorubicin was determined. The resting left ventricular ejection fraction before doxorubicin treatment was $52.9 \pm 5.0\%$ and increased significantly to $62.7 \pm 6.8\%$ with exercise ($p<0.001$); the resting left ventricular ejection fraction after doxorubicin treatment was $45.9 \pm 6.6\%$ and increased significantly to $51.4 \pm 7.7\%$ with exercise ($p<0.01$). Six of 7 patients increased the left ventricular ejection frac-

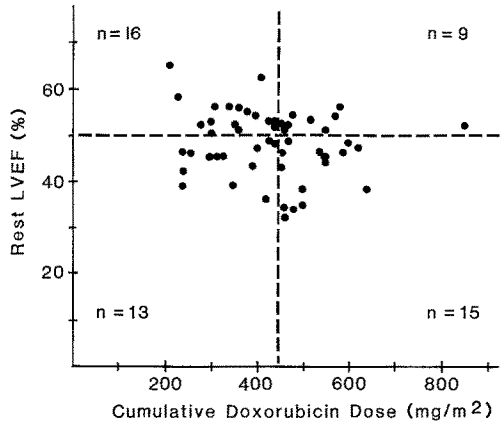

Fig. 1. Relationship between resting left ventricular ejection fraction (LVEF) and cumulative doxorubicin dose in 53 patients.

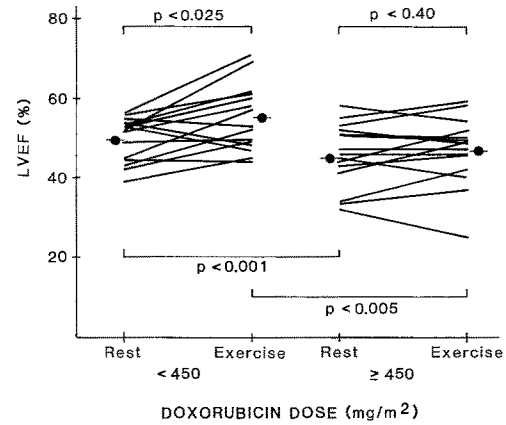

Fig. 2. Response of left ventricular ejection fraction (LVEF) to exercise in 30 patients. The patients were divided into two groups based on accumulated doxorubicin dose.

tion more than, or equal to, 5% during the baseline exercise test, while 5 of 7 increased more than, or equal to 5% during the second test. The heart rate response (120.4 ± 16.9 bpm vs 119.1 ± 17.8 bpm) and maximum work load (74.4 ± 17.2 watts vs 68.2 ± 23.2 watts) were not significantly different for both exercise tests.

Group II: Patients studied serially during treatment

In the 22 Group II patients, serial studies during treatment with doxorubicin were performed (Fig. 4). The resting left ventricular ejection fraction of initial studies was 53.1 ± 6.2%, and decreased to 46.9 ± 7.7% in follow-up studies ($p;<0.001$).

In 11 patients of this group, serial studies with exercise were performed. The resting left ventricular ejection fraction of the initial studies was 50.1 ± 6.0% and increased significantly to 57.3 ± 9.6% during exercise ($p<0.001$); the resting left ventricular ejection fraction of follow-up studies was 46.3 ± 6.8% and increased significantly to 50.1 ± 6.9% during exercise ($p<0.05$) which was significantly less than in the initial exercise study ($p<0.01$). Eight of 11 patients had a normal ventricular exercise response during the first study, 6 of 11 during the second study. There were no significant differences between both exercise tests in heart rate response (116.9 ± 17.7 bpm vs 113.6 ± 20.12 bpm) and work load (63.6 ± 23.4 watts vs 56.7 ± 25.4 watts).

Regional wall motion abnormalities

In the majority of our patients on doxorubicin treatment, regional wall motion abnormalities were observed, which were characterized in all cases by apical hypokinesis. The wall motion abnormality occurred post-treatment in 68% of the entire 53 patients studied at rest. The incidence of wall motion abnormalities was 55% (16 of 27 patients who received less than 450 mg/m^2 of doxorubicin), but 83% (20 of 22) in patients who received more than, or equal to, 450 mg/m^2 of doxorubicin. The wall motion abnormalities in the 30 patients with an exercise test occurred in 73% (22) at rest, and in 47% (14) during exercise. In the 15 patients who received less than 450 mg/m^2 of doxorubicin, the wall motion abnormality occurred in 57% (8) at rest and in 21% (3) during exercise. In the 15 patients who received more than 450 mg/m^2 of doxorubicin, the wall motion abnormality occurred in 87% (14) at rest and in 69% (11) during exercise.

No wall motion abnormality at rest was observed in the 14 Group I patients before doxorubicin treatment, but a wall motion abnormality at rest occurred in 93% (13) after doxorubicin treatment.

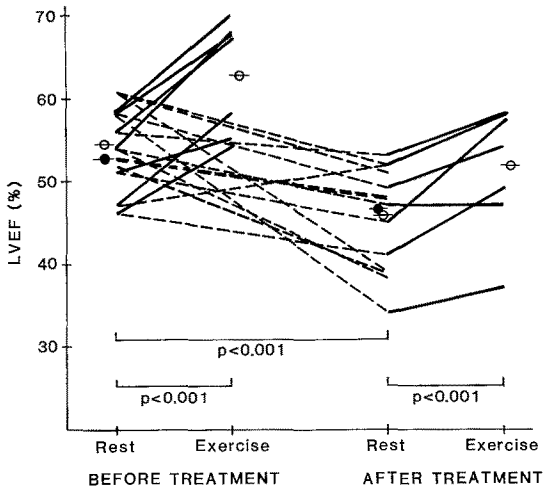

Fig. 3. Rest and exercise left ventricular ejection fraction in 14 Group I patients before and after doxorubicin treatment. Serial resting studies were performed in 14 patients (dotted line). Seven of these 14 patients underwent exercise before and after treatment (solid line).

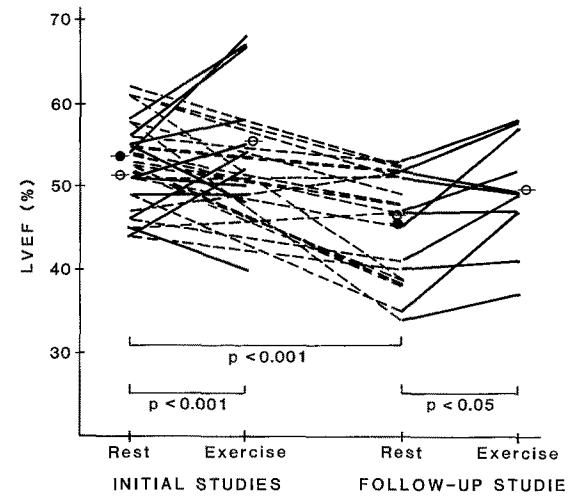

Fig. 4. Rest and exercise left ventricular ejection fraction in 22 Group II patients during doxorubicin treatment. Serial left ventricular ejection fractions at rest were determined in 22 patients during treatment (dotted line). Exercise studies (solid line) were performed in 11 of the 22 patients.

The wall motion abnormality at rest in 22 Group II patients occurred in 18% (4) in the initial studies and in 80% (20) in the follow-up studies.

Phase analysis

Phase analysis of images were performed for Group I and II patients to confirm the wall motion abnormality described visually. Phase analysis can be used to assess synchronicity of ventricular wall motion which is quantitated using the standard deviation of the left ventricular peak in the phase distribution histogram. In normals, the standard deviation of the left ventricular peak has been found to be below 12° at rest and 10° during exercise.

In 14 Group I patients, the standard deviation of the left ventricle before treatment was $9.6 \pm 1.7°$ at rest and increased significantly to $12.8 \pm 3.0°$ after doxorubicin treatment ($p<0.001$). For 7 patients with an exercise test before and after treatment, the standard deviation at exercise was unchanged with $9.9 \pm 1.7°$ before and 9.6 ± 1.9 after treatment (NS).

In 22 Group II patients, the standard deviation of the left ventricle on initial studies was $10.4 \pm 1.9°$ at rest and increased significantly to $12.5 \pm 3.1°$ on follow-up studies during doxorubicin treatment ($p<0.01$). In 11 patients with serial exercise testing, the standard deviation was $10.1 \pm 1.4°$ and $9.8 \pm 1.9°$ respectively during the two studies with exercise without significant difference (NS).

Discussion

The results of this study confirm earlier reports on the cardiotoxic effect of doxorubicin and its relationship to the cumulative dose of the drug [2–14]. The mean ejection fraction in the group receiving more than 450 mg/m^2 was significantly lower than in the group receiving less than 450 mg/m^2. However, the variation in ejection fractions for a given dose was considerable, these precluding a significant linear correlation between dose and ejection fraction. The left ventricular ejection fraction used in this study as well as in previous investigations as a parameter of left ventricular function does not directly reflect cardiac contractility, but rather the combined effect of preload, afterload and contractility. 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 left ventricular function.

In our patient population, 33 of 53 patients had an abnormal ejection fraction (<50%) 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/m^2, as compared to patients receiving less than 450 mg/m^2 (14/27). The data however show that in 20 of the 53 patients, the ejection fraction remained within normal limits and that some patients even maintained a normal ejection fraction after exposure to large doses of doxorubicin, indicating a considerable interindividual variation in the susceptibility to the cardiotoxic effect of doxorubicin.

In earlier reports it has been stated that exercise studies increase the sensitivity of early detection of doxorubicin induced cardiomyopathy [16, 19, 23, 38]. In the 30 patients undergoing treatment with doxorubicin, 14 had an abnormal exercise response, defined as a failure to increase LVEF by more than 5%. However, only three of these had a normal resting LVEF. Thus, in this group of patients, exercise added little diagnostic information for detection of abnormal ventricular function.

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 generally represent 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. None of the patients developed chest pain or ischemic ECG changes during exercise. 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.

With serial studies at rest, the effect of doxorubicin on LV function can be assessed more specifically since rapid development of coronary artery disease within a few months rarely occurs and changes of cardiac performance most likely reflect the effect of the therapeutic intevention. In the Group I patients studies before and after doxorubicin, 5 of 7 patients maintained a normal exercise response, with a new abnormal exercise response present in 2 of 7 patients. However, the resting ejection fraction decreased in 12 of 14 patients when the baseline value was compared with the post-treatment value. These data suggest that the change in resting function is more sensitive than the exercise response in detecting the toxic effects of doxorubicin. The same trend could be demonstrated in Group II patients with serial studies during treatment. Seven of 11 patients maintained a normal exercise response with 4 new abnormal responses, while 17/22 demonstrate a further decrease in resting function. Therefore, we conclude that serial determination of resting ejection fraction in patients receiving doxorubicin is most sensitive and specific for the evaluation of the cardiotoxic effect.

Regional left ventricular wall motion abnormalities are common in patients with coronary artery disease, but have also been described in patients with other cardiac diseases such as valvular heart disease and cardiomyopathies [39, 47–50]. Regional impairment of wall motion has, to our knowledge, not been reported in patients receiving doxorubicin treatment. In view of the relatively high incidence (68% at rest in 53 patients), silent coronary artery disease as the etiologic factor appears to be unlikely. In addition, the incidence of regional wall motion abnormalities decreased during exercise, a finding not consistent with ischemic heart disease. Wall motion abnormalities occurred more often in patients who received more than 450 mg/m^2 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 left 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 those 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 has been shown to cause dilatation of the heart [3, 5], changes in loading conditions could lead to a regional decrease of myocardial fiber shortening. During exercise and a concomitant increase of adrenergic stimulation, these regional differences in loading conditions may be overriden, and may explain the improvement of regional wall motion 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 in our study confirms a visual impression. We did find an increase of standard deviation in serial studies reflecting less synchrony of contraction. This finding paralleled the increased incidence of visually observed wall motion abnormalities. The standard deviation decreased during exercise, again consistent 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, standard deviation increased markedly during exercise [39]. The discrepancy between our findings and an ischemic phase pattern further suggests that the observed wall motion abnormalities are due to the effect of doxorubicin, and are not a consequence of coronary artery disease.

Conclusion

We conclude from this study that the cardiotoxic effect of doxorubicin can be monitored best 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. The results of phase analysis which allows objective assessment of synchrony of left ventricular wall motion supports the visual observation of regional wall motion abnormalities.

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