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Early Detection of Doxorubicin Cardiotoxicity by M-Mode Echocardiography

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Summary. *The influence of increasing doses of doxorubicin on the heart was examined in 30 patients with solid tumors, M-mode echocardiography being used to evaluate left ventricular contractility. The function of the left ventricle remained normal in 26 subjects, whereas four patients had evidence of cardiotoxicity after cumulative doses of 220, 380, 420, and 450 mg/m^2. Transient overt heart failure was noted in one subject only.*

Doxorubicin cardiotoxicity can be detected by M-mode echocardiography, a simple and non-invasive technique, prior to the appearance of overt congestive heart failure. Patients demonstrating left ventricular dysfunction are probably not canditates for receiving further therapy with anthracycline antibiotics. Limitation of M-mode echocardiography include a 28% incidence of inadequate studies in this group of patients, and a relative inaccuracy of the technique in evaluating patients with prior myocardial infarction.

Introduction

Cardiotoxicity is a serious complication of therapy with anthracycline antibiotics (doxorubicin and daunomycin), limiting the clinical use of these compounds [4, 8, 12, 15, 22]. Whether the occurrence of congestive heart failure (CHF) can be predicted and possibly prevented by measuring left ventricular (LV) function serially is unclear. In this study, we performed serial ultrasonic examinations of the heart in a group of patients receiving doxorubicin (adriamycin). It was our purpose to determine the influence of increasing doses of the drug on LV function, to characterize the evolution of patients demonstrating deterioration of LV function, and to draw conclusions concerning the need for performing serial evaluation of LV function in patients receiving anthracycline compounds.

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Materials and Methods

During a 15-month period starting in August 1976, we made a prospective study of 120 consecutive subjects with solid tumors started on doxorubicin. Prior to receiving doxorubicin, all 120 subjects underwent a clinical evaluation, including a 12-lead ECG and a chest X-ray, to assess their cardiovascular status. M-Mode echocardiography was performed with a Picker 80-C Echoview ultrasonoscope and a Honeywell 1856 recorder. Left ventricular dimensions were measured during end-diastole (at the beginning of the QRS deflection of the ECG) and during end-systole (at the narrowest systolic dimension), as illustrated in Fig. 1. The percent fractional shortening of the LV short axis (% FS) was calculated as

$$\frac{\text{LV end-diastole} - \text{LV end-systole}}{\text{LV end-diastole}}$$

and used as an index of LV contractility [13]. In the absence of regional LV contraction abnormalities, the % FS is a reliable index of LV function well suited to analysis of the diffuse cardiac damage caused by anthracycline antibiotics. In our laboratory, a % FS below 25% is considered evidence of reduced LV contractility. We planned to repeat the clinical evaluation, ECG and echocardiography after cumulative doses of approximately 100, 200, 300, and 400 mg/m^2 and to perform at least one study 3 months after the last dose. This aim was realized in only 30 subjects (group A) who had undergone at least three adequate echocardiographic examinations during therapy and who were followed up to a total doxorubicin dosage of at least 280 mg/m^2. The remaining 90 patients (group B) included 34 patients whose echocardiographic study was inadequate for evaluation of LV function, one patient without CHF, who was advised not to start doxorubicin therapy because of active coronary artery disease, and 55 patients for whom too few data were available for serial evaluation, for reasons such as early death from cancer and withdrawal from adriamycin therapy because of non-cardiac toxicity.

Group A

There were 12 males and 18 females with a mean age of 48.7 ± 3.3 years (SEM) (range 4–71 years). Tumor diagnosis is listed in

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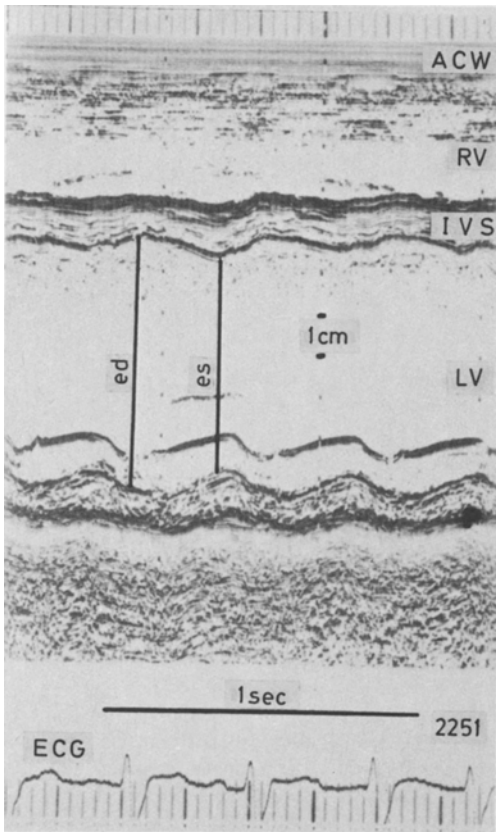

Fig. 1. Echocardiogram obtained in a patient with doxorubucin cardiotoxicity. The LV end-diastolic (ed) dimension is increased to 6 cm (normal value in adults is 3.0–5.3 cm). The % FS of the left ventricle (normal 25%) is reduced to 15%. There is a symmetric reduction of the contraction of the interventricular septum (IVS) and of the posterior wall indicating diffuse myocardial disease. ACW, anterior chest wall; RV, right ventricle; LV, left ventricle; ed, end-diastole; es, end-systole; P, pericardium

Table 1. Tumor diagnosis (group A)[a]

	n	*n* with LV dysfunction[b]
Breast	6	2
Ovary	3	0
Cervix uteri	3	0
Thyroid	2	0
Soft-tissue sarcoma	6	0
Lymphoma	6	1
Wilms' tumor	1	1
Others	3	0

[a] See text for definition of group A
[b] LV, left ventricle

Table 1. Seven patients had evidence of cardiovascular disease (Table 2) and two had diabetes. Mediastinal irradiation had been performed in nine subjects. All but five subjects received anti-tumoral chemotherapy before or during doxorubicin therapy. Group A patients received a mean total doxorubicin dose of 393.8 ± 13.9 mg/m^2. The mean total dose at the time of the last echocardiographic examination was 385.2 ± 13.7 mg/m^2 (range 220–540 mg/m^2). Echocardiographic follow-up lasted 5–26 months (mean of 9.4 ± 0.9 months) after the first dose of doxorubicin. One hundred sixtyseven adequate echocardiograms were available for evaluation.

Table 2. Prior cardiovascular disease (group A)

	n	*n* with LV dysfunction
Hypertension	4	0
ST-T changes on ECG	3	1
Angina pectoris	2	1
Old myocardial infarction	1	1
Past history of heart failure (due to thyrotoxicosis)	1	0
Ventricular premature beats	1	0
Total	7	1

Results

Group A

All subjects had a normal % FS and all but one had a normal LV end-diastolic dimension prior to receiving doxorubicin. In the entire group of 30 patients, no significant difference in mean LV size or function was noted between the pre-drug and the last treatment study (Table 3). Analysis of individual data showed two groups of patients.

1. Patients Whose LV Function Become Abnormal (Figs. 2 and 3)

The % FS fell below normal values in four patients, indicating a reduced LV contractility. Pertinent information concerning these four patients is presented in Table 4. The % FS of patient VS fell to 22% after a dose of 220 mg doxorubicin/m^3. Since her clinical examination and LV end-diastolic dimension were normal, doxorubicin administration was continued up to a cumulative dose of 450 mg/m^2. Her last planned dose (50 mg/m^2) was omitted because of evidence of further deterioration of LV function. Clinical heart failure or cardiac enlargement were never noted through out her clinical course. Reduced LV function was noted in patient HM after administration of 420 mg^2, doxorubicin/m^2, resulting in omission of her last planned dose (60 mg/m^2). Her last echogram, recorded 5 months after discontinuation of the drug, showed a normal % FS, indicating recovery of normal LV contractility. This patient died suddenly 2 months later, never having shown evidence of CHF. The only sign suggesting deteriorating

Table 3. Left ventricular size and function during doxorubicin therapy (group A, n = 30)

	Pre-drug	Post-drug	
Left ventricular end-diastolic dimension (cm)[a]	4.53 ± 1.09	4.62 ± 1.15	NS
Left ventricular fractional shortening (%)[a, b]	38.70 ± 1.50	36.17 ± 1.52	NS

[a] Values are given as mean ± SEM
[b] See text for definition of fractional shortening

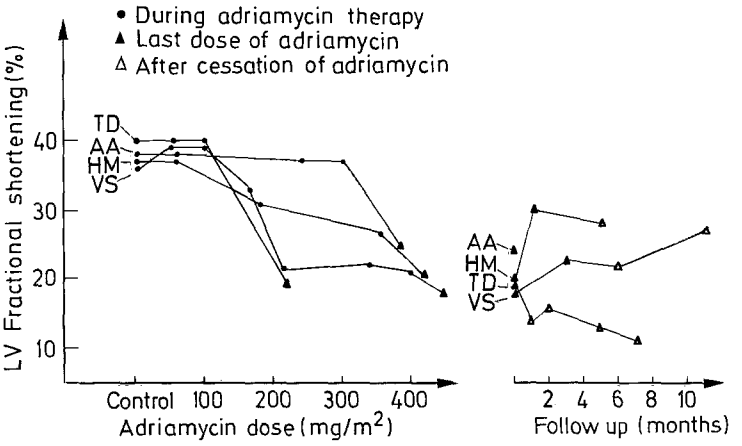

Fig. 2. Dose-related changes in LV contractility (as estimated by the % FS of the left ventricle) occurring in four patients with cardiotoxicity. *Right panel* shows changes in contractility after cessation of therapy in three patients for whom follow-up echocardiographic studies are available

LV function was a persistent sinus tachycardia. Depressed LV function was noted in patient AA after administration of 380 mg doxorubicin/m^2, prompting cessation of therapy; he died 2 months later of terminal cancer without clinical CHF. Patient TD, with a past history of diaphragmatic myocardial infarction and mild angina pectoris on effort, demonstrated reduced LV function after a dose of 220 mg/m^2. Though his cardiovascular status was normal, doxorubicin was stopped. Persistent sinus tachycardia was noted 1 month later, followed 3 months later by clinical CHF and echocardiograhic evidence of deteriorating LV function. When seen 13 months after his last dose, patient TD was free of CHF.

Except for patient TD, reduced LV function was initially associated with a normal LV end-diastolic dimension, and therefore the reduced % FS was entirely due to an increased LV end-systolic dimension.

2. *Patients Whose LV Function Remained Normal*

Twenty-six patients belonging to group A did not develop cardiotoxicity. Whereas quite large variations in LV function were noted during doxorubicin therapy (Fig. 4), the % FS of these subjects never fell below 25% and none developed clinical CHF.

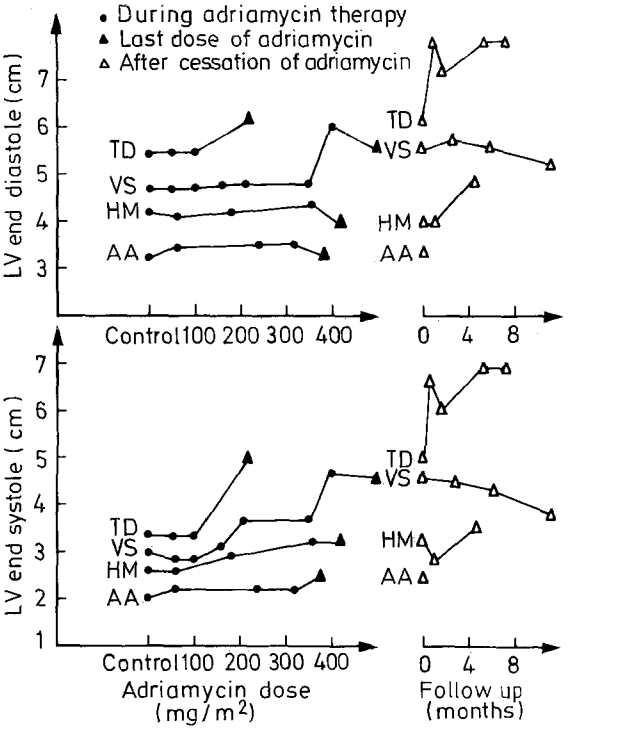

Fig. 3. *Upper panel,* dose-related changes in LV end-diastolic dimensions occurring in four patients with cardiotoxicity. *Lower panel,* dose-related changes in left ventricular end-systolic dimensions. *Right panels,* changes in LV dimensions following cessation of therapy

Table 4. Clinical characteristics of four patients with left ventricular dysfunction

Patient	Sex	Age	Tumor	Heart disease	Mediastinal irradiation (rads)	Doxorubicin dosage (mg/m^2)	Duration of therapy (months)	Follow-up (since start of therapy)
VS	F	64	Breast	0	3,300	450	7	Died after 30 months. No heart failure
HM	F	53	Breast	0	3,600	420	7	Transient pericardial effusion during therapy. Died after 14 months. No heart failure
AA	M	4	Wilms'	0	4,000	380	7	Died from cancer after 9 months. No heart failure
TD	M	66	Lymphoma	+	0	220	7	Alive after 20 months. Transient heart failure

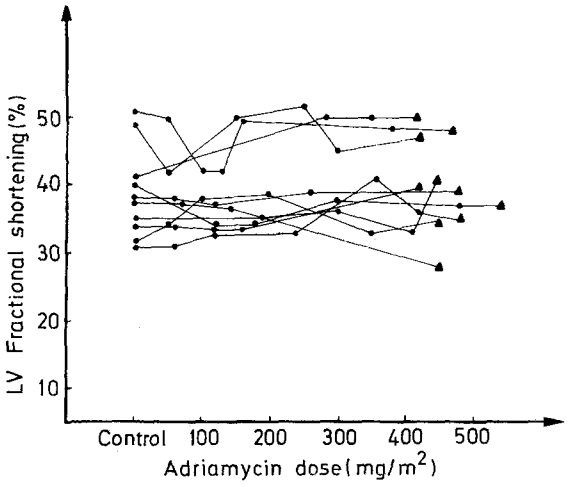

Fig. 4. Dose-related changes in LV fractional shortening in ten consecutive patients completing a course of at least 400 mg doxorubicin/m^2 without showing cardiotoxicity

Influence of Previous Therapy

a) Mediastinal Irradiation. Patients with mediastinal irradiation had a higher incidence of cardiotoxicity than patients who did not receive radiation (3 of 9 vs 1 of 21). The difference in frequency did not reach statistical significance ($P = 0.14$, Fisher's two tailed exact test).

b) Drug Therapy. No significant relationship was noted between therapy with cyclophosphamide (24 patients), 5-fluorouracil (7 patients), DTIC (5 patients), methotrexate (8 patients), or vincristine (17 patients) and the development of depressed LV function. A near-significant relationship evolved between the administration of prednisone and the appearance of depressed LV function. Thus, cardiotoxicity was seen in three of seven patients receiving prednisone, but in only one of 23 subjects not receiving steroid therapy ($P = 0.06$, Fisher's two-tailed exact test).

Group B

None of the 90 subjects in group B is known to have developed CHF. Many died from cancer before completing their planned doxorubicin course. All 170 adequate echocardiographic studies in this group showed normal LV size and function.

Influence of Coronary Artery Disease

Four of our 120 patients had a past history of myocardial infarction; all four had angina pectoris. Adequate echocardiographic examination was obtained in one subject only (TD). The second patient was not allowed to start chemotherapy because of unstable angina. The third received a cumulative dose of 400 mg/m^2 without ill effects, whereas the fourth died of cancer after receiving 110 mg/m^2 only. Angina pectoris without past infarction was present in one subject, who received a cumulative dose of 360 mg/m^2 without showing changes in LV function.

Discussion

Cardiotoxicity is the most serious complication limiting the use of anthracycline coumpounds. The occurrence of CHF is directly related to the amount of myocyte damage, which itself is proportional to the total cumulative dose administered [2, 5]. Recognition that anthracycline-induced CHF is dose-related had led to the recommendation that anthracycline dosage be limited to 450–550 mg/m^2 (or less in

patients thought to have an increased risk of developing cardiomyopathy) [4, 8, 12, 15, 22]. However, a small percentage of patients will develop overt CHF at an anthracycline dosage well below 550 mg/m^2, and about 50% of adults developing overt CHF will die of this complication [5]. At the same time, many patients requiring anthracycline doses of over 450–550 mg/m^2 for therapy of cancer are restricted to a lower dosage for fear of inducing CHF.

Depressed LV function can be detected prior to the appearance of overt CHF by either non-invasive or invasive techniques, such as echocardiography [3, 9, 18], quantitative radionuclide angiography [1, 19], cardiac catheterization [5], or endomyocardial biopsy [5]. The usefulness of measuring systolic time intervals or ECG voltage to detect early LV dysfunction is controversial. Many authors have proposed that serial measurements of LV function be used to monitor anthracycline effect on the heart and that therapy be stopped if and when evidence of reduced LV function develops [1, 3, 5, 9, 18, 19]. This approach is controversial [11], but might prevent individuals from developing cardiomyopathy at dosage below 450–550 mg/m^2, and might also allow individuals to receive anthracycline doses above 550 mg/m^2 safely.

We used echocardiography to study the influence of increasing dosage of doxorubicin on LV function. M-Mode echocardiography is a well-established, widely available technique, allowing evaluation of LV function at little cost and at no risk to the patient. Accurate assessement of LV function requires high-quality studies in the 'standard position' [16, 17], which could not be obtained in 28% of our 120 patients. This high incidence of inadequate studies is unusual in our experience [14], but is similar to that reported by Ewy in adult patients with cancer [9]. The presence of scarring on the chest from surgery or radiation and the common occurrence of marked tachypnea related to complications of cancer may have contributed to this relatively high failure rate. A much lower incidence of inadequate echocardiographic studies can be expected in a younger population [10] or in a population without chest disease.

Among our four patients with deteriorating LV function, one (HM) had a small pericardial effusion (less than 100 ml) noted during the pre-drug study only. Large pericardial effusions do occur in patients with disseminated carcinoma [7] and may prevent accurate assessement of LV function by M-mode echocardiography [21]. A large, persistent left pleural effusion was present in the same patient and may have altered her LV dimensions.

Cardiac metastasis occurs in 10–20% of patients dying with malignancy [7] and therefore the possibility that deterioration in LV function resulted from spread of the tumor to the heart, rather than from doxorubicin cardiotoxicity, should be considered. This possibility cannot be excluded in patient AA but is unlikely in the other three patients, since their depressed cardiac function eventually improved following cessation of doxorubicin therapy.

Mean values for % FS did not decrease significantly as the cumulative dose of doxorubicin was increased to a mean value of 385 mg/m^2. This finding is consistent with results reported by Ewy [9], but is in contrast to the results of other authors, who noted a significant decrease in indices, reflecting LV contractility with increasing cumulative anthracycline drug dosage [1, 3, 11, 18, 19]. This discrepancy may be related to a different patient population, drug dosage, and associated therapy, or may reflect a relative lack of sensitivity of M-mode echocardiography in detecting subtle changes in LV contractility.

Whereas LV function remained normal in 26 patients, evidence of cardiotoxicity appeared in four subjects. Persistent sinus tachycardia was the only clinical clue suggesting reduced LV function in two of these four patients. In accordance with other authors [15, 22], we did not find the ECG useful for early detection of cardiotoxicity. As noted by Singer [19], the reduction in contractility results from an increased LV end-systolic dimension. Therefore chest X-ray is usually not helpful in detecting early signs of LV dysfunction since the heart is not enlarged and since signs of pulmonary congestion are initially absent.

Whether early detection of LV dysfunction by M-mode echocardiography was beneficial can only be answered in a speculative way. It was the policy of the Oncology Department not to administer over 550 mg doxorubicin/m^2 and usually to restrict the dosage to 450 mg/m^2 at the time this study was performed. Since cardiotoxicity was detected close to the self-imposed dose limit of 450–550 mg/m^2 in three of the four subjects, the benefit of having detected sub-clinical LV dysfunction must have been limited. However, our fourth patient (TD) would have continued to receive doxorubicin for up to 3 months and more severe, possibly fatal CHF might have occurred, since every additional dose of doxorubicin increases the amount of myocyte damage [2, 5]. Patient TD had a past history of myocardial infarction and was the only subject with an abnormal pre-drug LV end-diastolic dimension. Examination by bi-dimensionnal echocardiography [6] or by quantitative radionuclide angiography [1, 19] might have revealed more extensive LV

damage than was initially shown by M-mode echocardiography.

Risk Factors

Previous mediastinal irradiation is a generally accepted risk factor for increased likelihood of developing doxorubicin cardiotoxicity [5, 15]. Our experience in this study is compatible with this view. Our results support the findings of Bristow, who did not find a relationship between administration of cyclophosphamide and higher risk of developing cardiotoxicity [5]. We were unable to confirm the findings of Smith suggesting DTIC as a separate risk factor [20], and did not assess enough elderly patients to comment on Bristow's claim that age over 70 is an independent risk factor [5]. We demonstrated a relationship between prednisone therapy and the development of cardiomyopathy, which was on the verge of significance. This finding has not been reported to our knowledge. Its significance is difficult to evaluate since all three patients treated with prednisone who developed cardiotoxicity also received other anti-tumoral drugs. Of seven patients with a prior cardiovascular disease who received a mean doxorubicin dose of 351 mg/m^2 only one, who had a past history of myocardial infarction, developed cardiotoxicity. Though prior myocardial damage is an accepted risk factor [15] we have shown that some patients with heart disease can receive therapeutic doses of doxorubicin without ill effects.

Conclusions

1) Despite its limitations, we believe that M-mode echocardiography is a simple and useful technique for monitoring of LV function in selected patients. Serial evaluation of LV function can detect patients with sub-clinical LV dysfunction who probably are at higher risk of developing CHF if therapy is not stopped [1].
2) Administration of anthracycline compounds without monitoring of LV function is probably acceptable if patients with evidence of significant myocardial damage are excluded and if dosage is limited to about 350 mg/m^2 for patients with risk factors and to about 450 mg/m^2 for those without risk factors. Whether patients without risk factors demonstrating a normal LV function after administration of 450 mg/m^2 may safely receive further therapy with doxorubicin is under investigation.
3) Patients demonstrating a reduced LV function (% FS below 25%) are usually not allowed to continue therapy with anthracycline derivatives until their % FS returns to normal values. Because of the 'recall effect' [15] such patients are not given further doxorubicin therapy unless a strong oncologic indication is present. Subjects with transient LV dysfunction receiving doxorubicin are studied prior to each subsequent drug administration.
4) Close cooperation between oncologist and cardiologist is essential for optimal therapy of patients receiving anthracycline compounds for the treatment of cancer.

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