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Noninvasive Methods for the Early Detection of Doxorubicin-Induced Cardiomyopathy

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Summary. Ninety-eight female patients (mean age 54 years) who underwent doxorubicin therapy because of metastatic breast cancer were submitted to radionuclide angiography at rest. Left ventricular ejection fractions (LVEFs) were found to decrease significantly with the increasing cumulative doxorubicin dosage. Patients with prior local radiotherapy showed lower LVEFs at the same dosage level than nonirradiated patients, but the difference was not statistically significant. In a further study, 52 patients (mean age 56 years) were followed up regularly for their history and systolic time intervals prior to each doxorubicin treatment course. Before starting treatment, LVEF values were normal in all cases. Fifteen of these patients complained of dyspnea at some time during the treatment period before the critical cumulative dosage level of 550 mg/m^2 was reached. Nine of these 15 patients showed an increase of the PEPI : LVETI ratio (≥ 0.40) and 12 patients a decrease of the LVEF values at rest at the same time. The rest of the patients did not complain of cardiac symptoms and did not show any significant alterations in systolic-time-interval measurements until the borderline dosage level (550 mg/m^2) was attained. To evaluate myocardial function with greater accuracy, these 15 patients were submitted to right-heart catheterization and radionuclide angiography at rest and during exercise. As a result, doxorubicin treatment had to be discontinued in three of these patients because of heart failure of stage III or IV and treatment with methyl digoxin and nifedipine was started. In these three patients cardiotonic medication could produce more or less complete cardiac recompensation.

We conclude from our findings that signs of stage-III heart failure in radionuclide angiography performed while the patient is at rest and exercising should be regarded as the upper limit of the therapeutic risk, where further doxorubicin treatment is contraindicated. Cardiotonic medication during cytostatic courses should be avoided, however, because the true functional condition of the myocardium could be masked during a potentially cardiotoxic therapy.

Key words: Doxorubicin cardiomyopathy – Systolic time intervals – Radionuclide angiography – Therapeutic risk

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Introduction

In the past 10 years, numerous patients with malignant disease have benefitted from doxorubicin therapy (Blum and Carter 1974). This anthracyclin is one of the most potent cytostatic drugs and has become irreplaceable in many chemotherapeutic combinations, no doubt for good reasons (Blum et al. 1980; Livingston et al. 1978; Salmon and Jones 1979). Regrettably, the application of the drug is limited on account of cardiomyopathies, which develop after chronic use (Lefrak et al. 1973). This author reported that congestive heart failure occurred in 30% of patients undergoing doxorubicin treatment at cumulative doses of >550 mg/m^2. In a further study, 59% of manifest heart failures were found to be fatal even if the drug was discontinued (Minow et al. 1975). For this reason, it was recommended that the cumulative dose should not exceed 550 mg/m^2 (Lefrak et al. 1973). However, if this general recommendation is obeyed as a matter of course, patients affected by drug-induced cardiomyopathy well below the critical dose level may be overlooked (O'Bryan et al. 1977), while patients who are unlikely to develop cardiomyopathies in spite of continued treatment may be prematurely withdrawn from what may be a vital drug for them. As the spectrum of available chemotherapeutic agents is limited and as there

are few alternatives to doxorubicin therapy, the use of objective methods for the early detection of cardiomyopathies and the timely discontinuation of treatment well before the patient's life is at risk is of great importance.

In the present study, an attempt was made to use noninvasive techniques for monitoring the cardiac condition of doxorubicin-treated patients, since the application of invasive methods for defining myocardial morphology and function is generally not feasible (Bristow et al. 1978, 1981).

Materials and Methods

In 98 female patients, aged between 32 and 69 years (mean age 54±7 years), undergoing cytostatic therapy for metastatic breast cancer, radionuclide angiography with the patients was done at rest. Fifty-three of them underwent local radiotherapy after mastectomy at a focal dose of 3,500–5,000 rad. In 45 patients radiotherapy was omitted. All patients underwent systemic anticancer treatment, which consisted of monthly courses of a combination of doxorubicin (40–60 mg/m^2 i.v. as short infusion) and cyclophosphamide (500–750 mg/m^2 p.o. or i.v.) with each infusion cycle. None of these patients had been given cardiotonics during the cytostatic courses. Cumulative doxorubicin doses dispensed to the different patient groups are summarized in Table 1. Radionuclide angiography tests were performed 4–12 weeks after the last doxorubicin infusion.

In another 52 female patients (mean age 56±9 years) histories and Systolic time intervals were consistently recorded prior to each cytostatic treatment course up to a cumulative dosage of 550 mg/m^2. At the beginning, radionuclide angiography at rest was done in all patients. At some time during the treatment, *15 of these patients* complained while at rest or exercising of dyspnea, which had not been present previously. In addition to systolic-time-interval measurement, radionuclide angiography at rest was done in these 15 patients at that time.

To evaluate their cardiac function more accurately, these 15 patients underwent radionuclide angiography and right-heart catheterization while at rest and exercising. The outcome of these extended cardiac examinations prompted cytostatic discontinuation and the institution of cardiotonic medication (0.3 mg methyl digoxin as maintenance dose and 30 mg nifedipine daily) for the treatment of cardiac failure *in three patients.* Each was followed up clinically. In one patient, hemodynamic studies while at rest and exercising were again carried out 4 weeks after the commencement of cardiotonic treatment and the discontinuation of cytostatic infusions.

For phonomechanocardiography, the most approved method was used (Weissler et al. 1969). Left-ventricular function was assessed on the basis of the ratio between preejection period and left-ventricular ejection time (PEPI: LVETI) corrected for the heart rate by the usual equations of regression (Stafford et al. 1970).

For radionuclide angiography, the steady-state method using in vivo Tc99m labeled red cells was employed (Ashburn et al. 1978; Bianco and Schafer 1979). After background correction, left-ventricular ejection fraction (LVEF) was computed by substraction of the counts over the end-diastolic from those over the end-systolic regions and by dividing the value obtained by the counts over the end-diastolic region (Digital Gamma 11 computer). Scanning was usually done in 45°LAO projection minus 10° caudal tilt.

Right-heart catheterization was done with the patient in supine position. A Baltherm dilution catheter was used for recording pulmonary arterial pressure and cardiac output. The heart rate (HR) was determined from the continuously recorded ECG; cardiac index (CI), stroke-volume index (SVI) and total peripheral resistance (TPR) were computed. Systemic blood pressure was obtained with the noninvasive Riva Rocci technique. Hemodynamic classification was done according to the usual directions (Reindell and Roskamm 1977).

Exercise testing was done by means of an electric brake-bicycle ergometer with the patient in supine position, beginning at a level of 25 and exercising for 3 min at each successive 25-step. Patients were expected to reach an exercising level of 50% of the minimal desirable performance (Bühlmann 1965; Samek and Roskamm 1980). The LVEFs and invasive hemodynamic parameters were recorded before each increase of the exercising level. Linear regression and analysis of variance were used for the statistical evaluation of the LVEF data at rest (Sachs 1972).

Table 1. Clinical details of 98 female patients with metastasizing breast cancer who were submitted to radionuclide angiography while at rest

Dosage group mg/m^2	Patient no.	Age (years)	Total dose of doxorubicin mg/m^2
Group I: with radiotherapy			
0	11	51.3±7.2	0
100	4	48.7±9.4	74.5±10.3
100–200	3	51.4±6.3	163.8± 5.4
200–300	9	58.7±4.1	270.1± 8.1
300–400	10	62.8±7.8	351.2±10.2
400–500	8	63.7±2.1	469.3±18.2
500–600	8	58.1±8.4	551.4±16.4
Group II: without radiotherapy			
0	13	60.1±9.1	0
100	2	56.2±7.1	60.0
100–200	1	38.0	180.0
200–300	6	50.7±4.1	287.8±10.4
300–400	9	53.3±7.4	372.1±16.2
400–500	7	56.4±4.1	479.7±16.4
500–600	7	56.1±8.0	548.3±10.1

Results

The resting ejection fraction obtained in 98 patients by radionuclide angiography was found to decrease significantly with the increasing cumulative doxorubicin dosage (Fig. 1). Given one and the same cytostatic pretreatment, patients who underwent local radiotherapy after mastectomy had a higher chance of showing below normal LVEFs (<50%) than those without radiotherapy (Fig. 2). The difference, however, was not statistically significant. Fifty-two patients were followed up at regular intervals for history and systolic-time-interval measurements up to a cumulative dosage level of 550 mg/m^2. Before starting doxorubicin treatment, symptoms of dyspnea were lacking and PEPI: LVETI and LVEF values were found to be normal in all patients. In the course of therapy, most of the patients ($N=43$) did not complain of cardiac symptoms and did not show significant alterations in systolic-time-interval measurements performed prior to each doxorubicin treatment schedule.

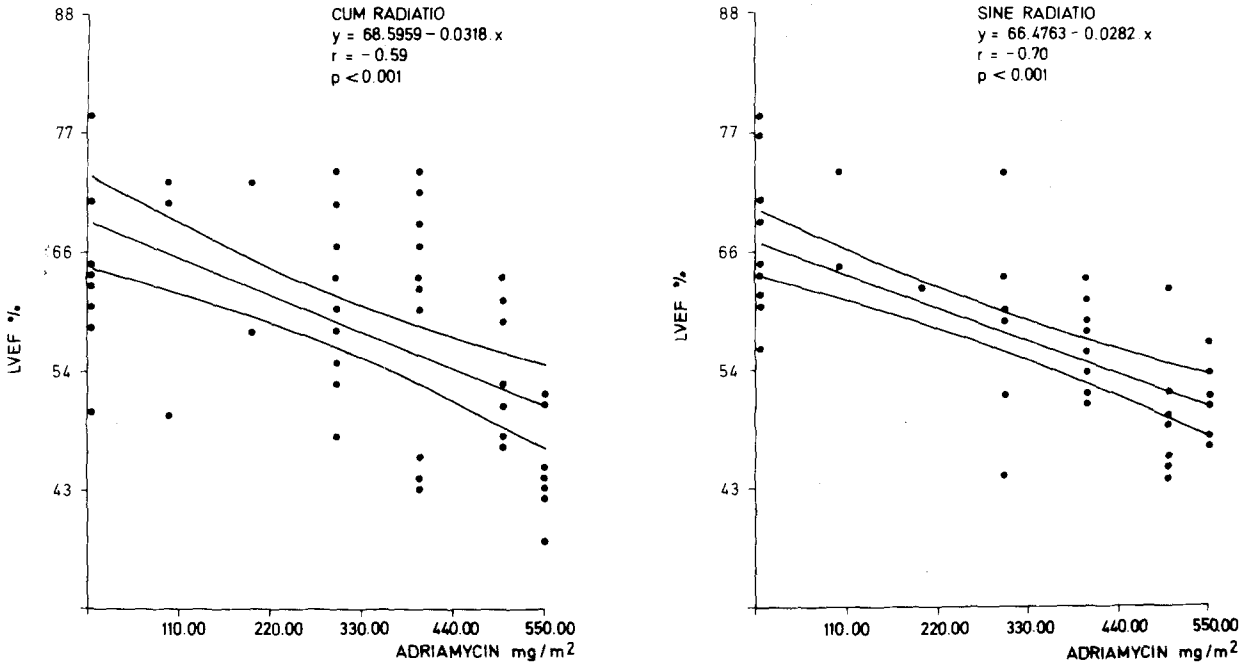

Fig. 1. Radionuclide angiography in patients at rest in doxorubicin-treated postoperatively irradiated ($N = 53$) and nonirradiated patients ($N = 45$) with metastatic breast cancer

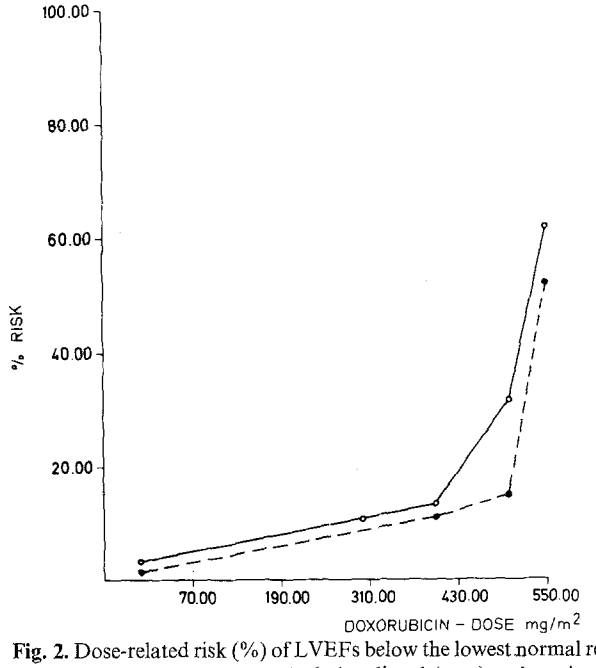

Fig. 2. Dose-related risk (%) of LVEFs below the lowest normal resting level of 50% in postoperatively irradiated (o–o) and nonirradiated patients (●–●) with metastatic breast cancer undergoing doxorubicin therapy

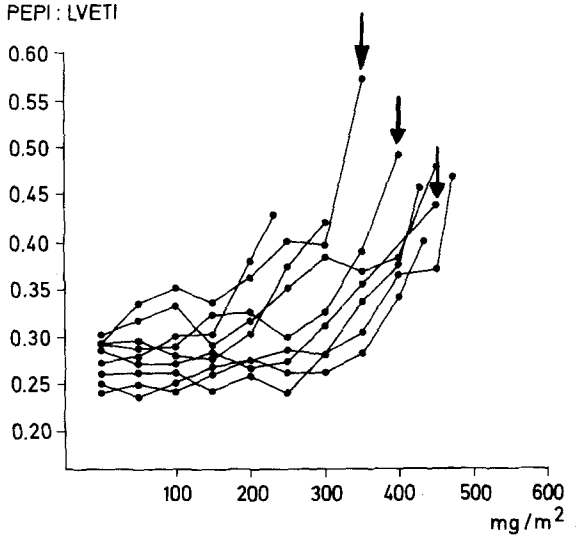

Fig. 3. Dose-related changes in systolic-time-interval measurements in nine patients with metastatic breast cancer before each doxorubicin treatment schedule. These patients were submitted to radionuclide angiography and right-heart catheterization at rest and during exercise. In three stage-III and -IV heart failure was found (↓)

Fifteen patients reported dyspnea while at rest or exercising at some time during the treatment period. One of these patients had clinical evidence of cardiac decompensation, i.e., leg swelling and signs of congestion on the chest Xray. In all others, the heart and chest X-ray films were found to be normal. Nine of these 15 patients showed an increase of the PEPI : LVETI ratio of $\geqq 0.40$ at the same time, although none of them had reached the critical cumulative dosage level of 550 mg/m^2 (Fig. 3). Twelve of these 15 patients showed decreased LVEF resting values at that time (Fig. 4).

To evaluate myocardial function with greater accuracy in these 15 patients, radionuclide angiography and right-heart catheterization were carried out with the

patient, at rest and exercising. Data are shown in Table 2. Although there was a history of clinical symptoms and although pulmonary metastases were ruled out by radiology, cardiac catheterization in 5 of these 15 patients showed an entirely normal heart function (stage 0) both at rest and during exercise. The LVEFs in these patients were normal at rest (> 50%) and increased appreciably during exercise, indicating again that cardiac function was normal. In 7/15 patients, mean pulmonary capillary wedge pressures (PCWP) during exercise were elevated (> 20 mm Hg), indicating stage-I heart failure. Radionuclide angiography at rest showed LVEFs to be normal in all but one patient. During exercise, LVEFs did not show any appreciable increase, but rather remained close to baseline. In only a single patient with a low resting LVEF value (47%) did the ejection fraction increase by 17% during exercise.

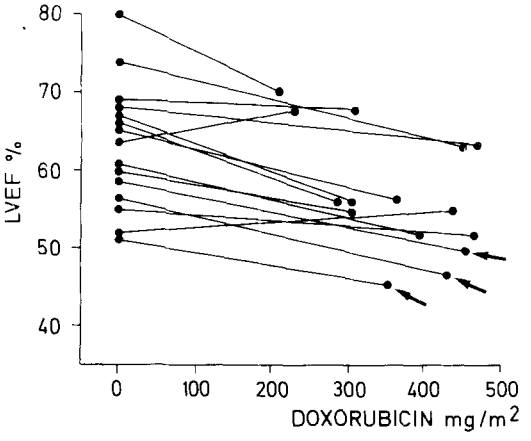

Fig. 4. Radionuclide angiography in 15 patients at rest with metastatic breast cancer prior and after discontinuation of doxorubicin therapy. In three stage-III and -IV heart failure was found (↓)

In $^{2}/_{15}$ patients, cardiac catheterization showed an inadequate increase in cardiac output during exercise and an abnormally high PCWP at rest (> 13 mm Hg) which is compatible with stage-III heart failure. On radionuclide angiography, resting LVEFs were below the lower limit of normal values in both cases (50%, 52%) and dropped substantially during exercise (42%, 47%).

The patient with clinical evidence of cardiac decompensation was found to have an elevated PCWP (16 mm Hg) and a reduced CI (2.11/min · m^2) on cardiac catheterization at rest which is consistent with stage-IV heart failure. For this reason, exercising was omitted. Radionuclide angiography revealed a resting LVEF of 46% in this patient.

On account of their hemodynamic data, the three patients with stage-III and -IV heart failure were excluded from doxorubicin therapy and started on methyl digoxin – 0.3 mg daily as maintenance dose – and 30 mg nifedipine daily. Within 3 weeks after commencing cardiotonic treatment, the patients' dyspnea had substantially improved clinically, as suggested by their histories. In the patient with stage-IV disease, the leg swelling had largely disappeared.

One patient underwent catheterization for a second time after an interval of 4 weeks (Fig. 5). This showed recompensation as reflected by the hemodynamic parameters: PCWP during exercise had dropped to within upper normal levels and cardiac output had increased

Table 2. Fifteen patients with metastatic breast cancer on doxorubicin and cyclophosphamide undergoing radionuclide angiography and right-heart catheterization for clinical symptoms or abnormal PEPI:LVETI

Patient	Age (years)	Total dose (mg/m^2)	Local radiation (rad)	PEPI:LVETI Pretreatment/ time of exercise testing	LVEF values (%)			Right-heart catheterization score[a]	Clinical staging[b]
					Rest	Exercise			
						20%	50%		
P.E.	43	300	0	0.32/0.39	55	60	60	0	1–2
D.T.	61	444	0	0.30/0.48	63	58	61	I	2
S.A.	62	235	0	0.27/0.43	68	63	64	I	1
J.H.	53	285	0	0.29/0.38	56	58	56	I	2
W.E.	72	457	0	0.31/0.32	52	52	51	I	2
L.R.	59	435	0	0.24/0.40	55	57	60	0	1
K.T.	69	360	0	0.22/0.37	56	54	56	I	2
B.M.	53	306	0	0.29/0.42	67	72	74	0	1
W.M.	49	300	5,000	0.32/0.39	55	61	61	0	1–2
W.A.	62	464	4,500	0.26/0.47	63	58	60	I	2–3
P.E.	50	384	5,000	0.29/0.49	52	52	47	III	3
L.J.	65	200	4,500	0.31/0.36	70	70	75	0	2
R.A.	49	350	5,500	0.29/0.57	46	–	–	IV	3
W.E.	59	425	5,000	0.25/0.45	47	57	55	I	2
A.L.	54	450	4,500	0.28/0.44	50	45	42	III	2

[a] According to the hemodynamic classification by Reindell and Roskamm (1977)
[b] Dyspnea: stage 1, walking up stairs; stage 2, walking on a flat surface; stage 3, at rest

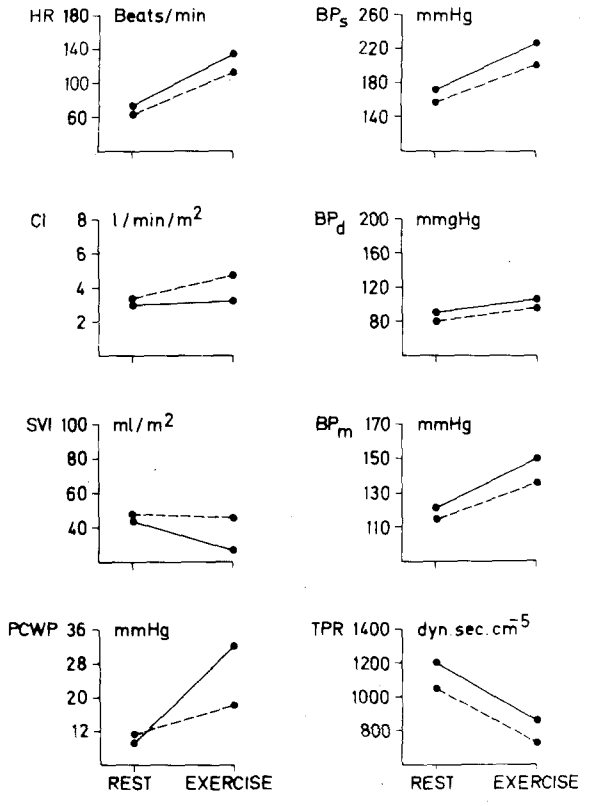

Fig. 5. Cardiac catheterization in a patient with metastatic breast cancer after discontinuation of doxorubicin infusions before (●–●) and 4 weeks after (●–●) cardiotonic treatment with methyl digoxin and nifedipine

substantially. At the same time, both the systolic and diastolic blood pressures had clearly decreased together with total peripheral resistance. Now after a period of 4 months, two of these three patients are still alive without signs of severe heart failure and are still in remission. One patient developed progressive metastatic disease after discontinuation of doxorubicin treatment and died of rapidly growing liver metastases 7 weeks later.

Discussion

In many centers, doxorubicin is administered up to a cumulative dose of 550 mg/m^2 without any cardiac monitoring of the patients. This is, however, inadequate, as some patients tend to develop doxorubicininduced cardiomyopathies well before the critical dosage level is reached (O'Bryan et al. 1977; Cortes et al. 1978). In addition, the discontinuation of the drug without hard evidence of cardiac dysfunction as soon as the critical dosage level is reached puts all those patients at a disadvantage for whom doxurubicin is the only treatment left. Currently accepted therapeutic recommendations have been criticized for their generalizing approach which leaves little scope to individual physiologic and pathologic variations. In the light of these inadequacies, a suitable procedure is needed which combines acceptable equipment and staff requirements with a large measure of safety in carrying out an individualized treatment. This procedure should allow identification of early cardiomyopathies developing before the critical cumulative dosage level of 550 mg/m^2 is reached to prevent life-threatening situations, while at the same time providing an exhaustive treatment in keeping with myocardial function. Current evidence of the pathogenetic mechanisms involved in the development of drug-induced cardiomyopathy (Bühner et al. 1980; Goormaghtigh et al. 1980; Lenzhofer et al. 1983b) suggests that the myocardium is damaged more and more by each infusion. The damage done is not life threatening as long as ventricular preload and heart rate can be increased to the point of ensuring an adequate pumping capacity of the myocardium and, as a result, an adequate oxygen transport. If this is precluded by treatment-related insufficiency of an excessively large number of fibers, manifest cardiac decompensation with its visible signs and symptoms will develop. In the light of these mechanisms, it seems appropriate to postulate that the upper limit of the therapeutic risk in doxorubicin-treated patients with metastatic cancer is reached as soon as stage III heart failure is detected. This, in fact, would constitute a contraindication to further treatment.

In the present study, a statistically significant correlation was found to exist between resting LVEFs and the cumulative doxorubicin dose in irradiated and nonirradiated patients (Fig. 1). Patients with prior irradiation treatment in general had lower LVEF values than nonirradiated patients at the same dosage level. However, statistical evaluation could not prove radiation treatment as an important risk factor in this particular study. Evaluation of cardiac function in the course of doxorubicin treatment by means of systolic-time-interval measurements is highly valuable (Lenzhofer et al. 1983a; Shuman et al. 1981). In this study, 52 patients were prospectively followed up by recording their history and systolic-time-interval measurements. Before the cumulative dosage level of 550 mg/m^2 was reached, 15 patients complained of dyspnea (Table 2) nine showed an increase of PEPI: LVETI >0.40 (Fig. 3), and 12 patients proved to have moderate decrease of LVEF at rest (Fig. 4). In right-heart catheterization, only three of these patients exhibited stage-III or -IV heart failure. If systolic-time-interval measurements had been the only method for defining the upper limit of therapeutic risk, six patients would have been discontinued from doxorubicin treatment although no severe heart failure would have been present.

Radionuclide angiography with the patient at rest is generally used for early detection of doxorubicin-in-

duced cardiomyopathy (Morgan et al. 1981). Since serial measurements of resting LVEFs in the course of doxorubicin treatment cannot give sufficient information about the true functional reserve of a patient's myocardial capacity, it appeared reasonable to submit all patients with clinical symptoms to a radionuclide angiography exercise test, as usually done in patients with coronary heart disease (Borer et al. 1979; Brady et al. 1979). However, exercising at adequate exercise levels as a problem in our study population, because many patients with metastatic disease had reduced muscle capacity. For the purposes of this study, patients were encouraged to exercise at 50% of the desired (level as indicated in pertinent tables rather than until exhaustion (Samek and Roskamm 1980). To obtain a better idea of the ejection fraction, at least two exercise levels were used. Since radionuclide angiography exercise testing has not been used to a large extent for this particular indication until now, we also performed right-heart catheterization with the patient at rest and exercising in order to have an acknowledged reference technique.

Although the relatively small number of patients examined does not allow any definitive conclusions to be drawn, the different hemodynamic stages of heart failure were found to be associated with different resting and exercising LVEFs (Table 2). To define the upper limit of the therapeutic risk, the presence of stage-III heart failure is the most important factor. In radionuclide angiography, this stage was characterized by a normal LVEF at rest, which tended to decrease during physical exercise. Stage-IV was tantamount to cardiac decompensation at rest with an abnormal resting LVEF. Patients with stage-I disease, by contrast, failed to adequately increase their LVEF during moderate exercising as subjects with normal myocardial function would (Borer et al. 1979). The LVEF rather remained close to the preexercising level. In our view, this stage of heart failure does not yet constitute an absolute contraindication for doxorubicin in patients with metastatic disease, because this stage, while associated with an abnormal increase of PWCP during exercise, is not characterized by functionally insufficient myocardial work. In patients undergoing adjuvant doxorubicin therapy, much more stringent criteria should, however, be used for defining contraindications, i. e., these patients should have entirely normal cardiocirculatory function (stage 0).

In this study it was exclusively patients with prior radiation treatment who developed severe heart failure (Table 2). Although the fraction of damage produced by radiotherapy cannot be calculated exactly in these few patients, this observation emphasizes the necessity for accurate cardiac surveillance especially in irradiated patients.

The problem of reversability of drug-induced cardiomyopathy is still not solved. In this study, we could show in three cases that the discontinuation of the drug as soon as hemodynamic stage-III disease was seen was well timed, because the institution of cardiotonic medication after drug withdrawal was found to produce more or less complete cardiac recompensation both by clinical and hemodynamic evidence (Fig. 5). None of our patients subjected to cardiotoxic treatment received cardiotonic medication as long as they were on the toxic drug. In our view, the concomitant administration of digitalis preparations, as recommended for preventing cardiotoxicity (Gupta et al. 1976; Williams 1978) could mask the true extent of myocardial damage and, as a result, delay the timely discontinuation of the cardiotoxic drug. In addition prophylactic digitalization would deny patients actually developing heart failure the benefits of the most effective cardiotherapeutic agent and should, therefore, be avoided as long as cardiotoxic treatment is applied.

The proposal to use objective criteria offering adequate safeguards for patients to be treated with doxorubicin is well justified and constitutes an essential element in deciding for or against chemotherapy involving doxorubicin. On the basis of our past experience, we have, therefore, developed a procedure which can be expected to help prevent the occurrence of life-threatening conditions due to drug induced cardiomyopathy.

1. For routine cardiac monitoring of patients without any special risk factors undergoing doxorubicin therapy, recording the history and evaluating the ECG and the systolic time intervals (PEPI:LVETI) is sufficient as long as the critical cumulative dose of 550 mg/m^2 reported in the literature (Lefrak et al. 1973) has not been reached.

2. If in the course of treatment dyspnea occurs that cannot be related to pulmonary origin (metastasis, lymphangiosis, effusion) or if the PEPI:LVETI ratio increases beyond 0.40, radionuclide angiography with the patient at rest and doing physical exercise should be ordered.

3. The persence of stage-III heart failure marks the upper limit of therapeutic risk of doxorubicin-induced cardiomyopathy and should prompt the discontinuation of scheduled doxorubicin courses.

4. If clinically indicated, cardiotonic medication should be started after rather than before withdrawal of the cytostatic drug.

References

Ashburn WL, Schelbert HR, Verba JW (1978) Left ventricular ejection fraction – a review of several radionuclide angiographic approaches using the scintillation camera. Prog Cardiovasc Dis 20:267–284

Bianco AJ, Schafer RB (1979) Radionuclide methods in the assessment of left ventricular function. Am J Med Sci 277:244–254

Blum RH, Carter SK (1974) Adriamycin: A new anticancer drug with significant clinical activity. Ann Intern Med 80:249–259

Blum RH, Corson JM, Wilson RE, Greenberger JS, Canellos GP, Frei E (1980) Successful treatment of metastatic sarcomas with cyclophosphamide, adriamycin, and DTIC (CAD). Cancer 46:1722–1726

Borer JS, Kent KM, Bacharach SL, Green MV, Rosing DR, Seides SF, Epstein SE, Johnston GS (1979) Sensitivity, specificity and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease. Comparison with exercise electrocardiography. Circulation 60:572–580

Brady TJ, Thrall JH, Clare JM, Rogers WL, Lo K, Pitt B (1979) Exercise radionuclide ventriculography: practical considerations and sensitivity in coronary artery disease detection. Radiology 132:697–702

Bristow MR, Mason JW, Billingham ME, Daniels JR (1978) Doxorubucin cardiomyopathy: evaluation by phonocardiography, endomyocardial biopsy, and cardiac catheterization. Ann Intern Med 88:168–175

Bristow MR, Mason JW, Billingham ME, Daniels JR (1981) Dose-effect and structure-function relationships in doxorubicin cardiomyopathy. Am Heart J 102:709–718

Bühlmann A (1965) Klinische Funktionsprüfung des Herzens. Schweiz Med Wochenschr 95:1327–1332

Bühner R, Bidert S, Miura D (1980) Erhöhung des frei-ionisierten zytoplasmatischen Calciums als Ursache der Adriamycin-Kardiomyopathie. Klin Wochenschr 58:747–748

Cortes EP, Gupta M, Chou C, Amin VC, Folkers K (1978) Adriamycin cardiotoxicity: early detection by systolic time interval and possible prevention by coenzyme Q_{10}. Cancer Treat Rep 62:887–891

Goormaghtigh E, Chatelain P, Caspers J, Ruysschaert JM (1980) Evidence of a specific complex between adriamycin and negatively-charged phospholipids. Biochim Biophys Acta 597:1–14

Gupta M, Cortes EP, Mundia A (1976) Systolic time interval (STI) in adriamycin (ADM) treated patients on digoxin or prednisone cardioprophylaxis. Proc Am Assoc Cancer Res ASCO 17:269–272

Lefrak EA, Pitha J, Rosenheim S, Gottlieb J (1973) A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 32:302–314

Lenzhofer R, Dudczak R, Dittrich C, Gumhold G, Moser K, Spitzy KH (1983a) Systolische Zeitintervallmessung zur Überwachung der Herzfunktion unter Adriamycintherapie bei Patientinnen mit metastasierten Mammakarzinomen. Dtsch Med Wochenschr 20:771–775

Lenzhofer R, Magometschnigg D, Dudczak R, Bolebruch C, Moser K (1983b) Indication of reduced doxorubicin-induced cardiac toxicity by additional treatment with antioxidative substances. Experientia 39:62–64

Livingston RB, Moore TN, Heilbrunn L, Bottomley R, Lehane D, Rivkin SE, Thigpen T (1978) Small-cell carcinoma of the lung: combined chemotherapy and radiation: a Southwest Oncology Group study. Ann Intern Med 88:194–199

Minow RA, Benjamin RS, Gottlieb JA (1975) Adriamycin (NSC-123127) cardiomyopathy: An overview with determination of risk factors. Cancer Chemother Rep 6:195–201

Morgan GW, McIlveen BM, Freedman A, Murray IPC (1981) Radionuclide ejection fraction in doxorubicin cardiotoxicity. Cancer Treat Rep 65:629–638

O'Bryan RM, Baker LH, Gottlieb JA, Rivkin SE, Balcerzak SP, Grumet GN, Salmon SE, Moon TE, Hoogstraaten B (1977) Dose response evaluation of adriamycin in human neoplasia. Cancer 39:1940–1948

Reindell H, Roskamm H (1977) Herzkrankheiten-Pathophysiologie, Diagnostik, Therapie. Springer, Berlin Heidelberg New York

Sachs L (1972) Statistische Auswertungsmethoden, 3. Auflage. Springer, Berlin Heidelberg New York

Salmon SE, Jones SE (1979) Studies of the combination of adriamycin and cyclophosphamide (alone or with other agents) for the treatment of breast cancer. Oncology 36:40–47

Samek L, Roskamm H (1980) Das Belastungs-EKG. In: Csapo G (ed) Konventionelle und intracardiale Elektrokardiographie. Documenta Geigy

Shuman RD, Ettinger DS, Abeloff MD, Livengood SV, Fortuin NJ (1981) Comparative analysis of noninvasive cardiac parameters in the detection and evaluation of adriamycin cardiotoxicity. Johns Hopkins Med J 149:57–63

Stafford RW, Harris WS, Weissler AM (1970) Left ventricular systolic time intervals as indices of postural circulatory stress in man. Circulation 41:485–492

Weissler AM, Harris WS, Schoenfeld CD (1969) Bedside technics for the evaluation of ventricular function in man. Am J Cardiol 23:577–583

Williams CJ (1978) Doxorubicin cardiotoxicity: role of digoxin in prevention. Br Med J 1:176

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