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Original Paper

Myocardial Function in Children and Adolescents after Therapy with Anthracyclines and Chest Irradiation

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Cardiotoxicity is a potential adverse effect of anthracycline (A) therapy. Radiotherapy (XRT) may also cause a variety of cardiac complications. The purpose of the present study was to evaluate these cardiac side-effects in children and adolescents treated for cancer. We assessed the cardiac status of 91 patients, divided into three groups: Group A ($n = 53$) had anthracyclines at a mean cumulative dose of 410 mg/m^2, group A+XRT ($n = 26$) had both chest irradiation (XRT) and A (mean 360 mg/m^2), and group XRT ($n = 12$) had XRT alone. The patients differed from the controls in both systolic and diastolic indices of myocardial function. In echocardiography, the left ventricular (LV) contractility was abnormal in 32% in group A, in 50% in group A+XRT, and in 8% in group XRT. In radionuclide cineangiography, the LV ejection fraction was subnormal in 19% in group A, in 24% in group A+XRT, and in 1 patient in group XRT. A higher cumulative dose of A predicted decreased contractility. Treatment with A and/or XRT often leads to cardiotoxicity. Although in most cases this cardiotoxicity seems to be mild and subclinical, the long-term clinical sequelae merit further evaluation.

Key words: anthracyclines, radiotherapy, childhood cancer, myocardial function, echocardiography, radionuclide cineangiography

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INTRODUCTION

WHILE AGGRESSIVE anticancer therapy in paediatric oncology is becoming more and more successful in terms of survival, more emphasis should be placed on adverse effects and late complications of therapy. Anthracyclines are effective cytostatic drugs included in many intensive anticancer chemotherapy regimens. Their most feared adverse effect is cardiomyopathy, the incidence and severity of which depend on the cumulative dose [1–9]. Tolerance of anthracyclines is individual [6, 7], and cardiomyopathy may progress for years after discontinuation of therapy [8–10]. In addition, chest irradiation may add to the cardiac side-effects of anthracyclines [4]. The major problem is in estimating a safe cumulative dose for the individual. In most studies, the incidence of congestive heart failure (CHF) after anthracycline therapy varies from 2 to 9% [6–8].

Multiple cardiac abnormalities, including decreased systolic left ventricular function, have been reported years after therapeutic irradiation [11–16]. Previous studies have indicated that the severity of the changes is correlated with the dosage and the fractionation of the radiotherapy.

Electrocardiography (ECG), systolic time intervals, chest X-ray, echocardiography [8–10, 14], and radionuclide cineangiography [14, 17–19] have all been used in cardiac evaluation during and after cancer therapy. An optimal method for cardiac evaluation should be non-invasive, repeatable and independent of loading conditions.

The purpose of the present study was to evaluate the cardiac side-effects of anthracyclines and chest irradiation therapy in children and adolescents treated for cancer by utilising non-invasive methods including chest X-ray, echocardiography and radionuclide cineangiography.

PATIENTS AND METHODS

Patients

At the Children's Hospital, University of Helsinki, Finland, from 1979 to 1990, 110 patients survived treatment with anthracyclines exceeding 300 mg/m^2, or chest irradiation with or without the use of anthracyclines. Of these patients, 91 were examined in this follow-up study in 1990–1992. At follow-up, the ages of the patients (58 males and 33 females)

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ranged from 5 to 24 years. Median follow-up after discontinuation of anthracycline therapy and/or irradiation was 4 (range, 1–12.3) years. All patients were in remission, off anticancer therapy, clinically asymptomatic (had no symptoms or signs of congestive heart failure) and euthyroid, and had a haemoglobin concentration of at least 10 g/dl.

The underlying diagnoses were as follows: acute lymphoblastic leukaemia (ALL) ($n = 27$); non-Hodgkin lymphoma ($n = 19$); Hodgkin's disease ($n = 13$); soft tissue sarcoma ($n = 12$); Wilms' tumour ($n = 9$); osteosarcoma ($n = 6$); acute myelogenous leukaemia ($n = 1$); Ewing's sarcoma ($n = 1$); glioma of the spinal cord ($n = 1$); Askin tumour ($n = 1$); and hepatoblastoma ($n = 1$).

The anthracycline drug used was doxorubicin. Some patients with ALL and non-Hodgkin lymphoma also received daunorubicin as part of their protocol. The cumulative dose was calculated as the sum (mg) of doxorubicin and daunorubicin/m^2. The dose rates were variable during the study period, ranging from slow intravenous (i.v.) bolus to 24-h infusion.

The radiation therapy (XRT) consisted of upper mantle irradiation for patients with Hodgkin's disease ($n = 13$), irradiation of the upper mediastinal mass for patients with NHL ($n = 14$), whole lung irradiation for pulmonary metastases of Wilms' tumour ($n = 6$) or soft tissue sarcoma ($n = 2$), irradiation of the thoracic spinal area for spinal cord glioma ($n = 1$), whole chest irradiation for intrathoracic sarcoma ($n = 1$), and half-chest irradiation for a massive Askin tumour ($n = 1$). The heart was not protected during irradiation. Normal fractionation methods were employed. Radiotherapy was administered once a day, 5 days a week, in 150–200 cGy fractions. All patients were treated at the unit of Radiation Oncology, University of Helsinki.

In order to examine the effect of anthracyclines and chest irradiation on cardiac function, we divided the patients into three groups (Table 1).

Group A consisted of 53 patients who had received anthracyclines at a cumulative dose exceeding 300 mg/m^2. The median cumulative dose was 410 (range 300–750) mg/m^2.

Group A+XRT consisted of 26 patients treated with anthracyclines and chest irradiation. They had all received irradiation of the mediastinum or the left lung, so that at least part of the heart had been irradiated. In this group, the median cumulative dose of anthracyclines was 360 (range 180–550) mg/m^2. The median dose of XRT for the thoracic area (left lung, mediastinum) was 24 (range 11–51) Gy.

Group XRT consisted of 12 patients who had had chest irradiation only. None had received any anthracyclines. The median dose of XRT to the thoracic area (left lung, mediastinum) was 40 (range 36–50) Gy.

Control subjects

The control group consisted of 38 children and young adults, 10 of whom were healthy children and 28 who were newly diagnosed, untreated cancer patients with no other systemic abnormalities (i.e. normal haemoglobin concentration, normal fluid and electrolyte balance, no evidence of infection, no pericardial effusion, no tumour mass in the thoracic area). The newly diagnosed cancer patients did not differ at all from the healthy control children in echocardiography, ECG or chest X-ray, and we therefore felt justified in combining these into a single control group. The median age of the controls was 10 (range 4–22) years. There were 20 boys and 18 girls. The healthy children underwent echocardiography only, whereas the newly diagnosed cancer patients had both echocardiography and radionuclide cineangiography.

Methods of cardiac evaluation

Chest X-rays. Chest radiographs were obtained to allow measurement of heart volume relative to body surface area [20], and pulmonary venous congestion. The chest X-rays were interpreted by a radiologist who was unaware of the other data of cardiac evaluation.

Echocardiography. Each patient was studied by echocardiography at a median of 4 (range 1–12.3) years after discontinuation of therapy. All studies were carried out by the same observer. M-mode recording was performed from the parasternal short axis view on a level just below the anterior mitral valve leaflet. An M-mode echocardiogram directed by two-dimensional echocardiography was recorded simultaneously with a phonocardiogram showing the aortic component of the second heart sound, an indirect carotid pulse tracing, and an ECG. Blood pressure was measured with a Dinamap automated vital-signs monitor (Criticon Inc., Tampa, Florida, U.S.A.).

Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) dimensions and left ventricular posterior wall thickness were measured. The relationship between LVEDD and the cube root of the body surface area (BSA) has been shown to be linear [21]. LVEDD was corrected for differences in body surface area according to: $LVEDD_{(corr)} = LVEDD / (BSA)^{1/3}$ [10, 21]. The relationship between the thickness of the LV posterior wall in end-diastole (PW_{ed}) and the square root of the body surface area has been shown to be linear [21]. The PW_{ed} was corrected for differences in BSA according to: $PW_{ed(corr)} = PW_{ed} / (BSA)^{1/2}$ [21]. These corrections were only used in the estimation of the left ventricular size and the thickness of the LV posterior wall in end-diastole but not in further calculations (see below).

Overall, left ventricular performance reflects the interplay

Table 1. Characteristics of the subjects in the study groups

Group	*n*	*f/m*	Age at study (years) median (range)	Follow-up after discontinuation of therapy (years) median (range)	Cumulative dose of anthracyclines (mg/m^2) median (range)	XRT dose (Gy) median (range)
A	53	21/32	14 (6–24)	3.5 (1–12.3)	410 (300–750)	0
A+XRT	26	10/16	14 (8–23)	4.0 (1.0–8.0)	360 (180–550)	24 (11–51)
XRT	12	3/9	19 (6–24)	7.3 (1.0–10.8)	0	40 (36–50)
Controls	38	18/20	10 (4–22)	—	0	0

of preload, afterload, heart rate and contractility. In dilated cardiomyopathy, the left ventricular systolic and diastolic dimensions are increased and the left ventricular wall is thin. This results in a much higher wall stress for the dilated ventricle as compared to a normal ventricle. In addition, contractility is decreased. The traditional indices of left ventricular performance, such as left ventricular fractional shortening (FS) and ejection fraction (EF), do not detect these changes at an early stage of dilated cardiomyopathy, neither do they distinguish between changes in contractility and alterations in loading conditions. Therefore, we chose to use a method independent of preload and afterload for the echocardiographic evaluation of left ventricular systolic performance. FS was calculated as the ratio of the difference between the LVEDD and the LVESD to the LVEDD: FS = (LVEDD –LVESD)/LVEDD. The rate-corrected velocity of fibre shortening (V_{cfc}) was calculated by dividing FS by rate-corrected ejection time. As an index of afterload, we calculated the left ventricular end-systolic wall stress [22]. This is directly proportional to the left ventricular end-systolic pressure (*P*) and diameter (LVESD), and inversely proportional to the thickness of the posterior wall in end-systole (PW_{es}):

$$\text{Wall stress} = \frac{(1.35)(P)(\text{LVESD})}{(4)(PW_{es})(1+PW_{es}/\text{LVESD})}$$

According to Colan and coworkers, the relationship between V_{cfc} and the left ventricular end-systolic wall stress is a measure of contractility independent of preload and afterload [23, 24]. We plotted our data on their published normal range [23], and expressed the deviation from the mean curve in standard deviation (S.D.) scores, using this as a unit of measurement in the individual subjects.

Diastolic function reflects the relationships between the left atrial and the left ventricular diastolic pressures and volumes. Derangements in the diastolic properties of the left ventricle contribute significantly to the clinical manifestations of congestive heart failure. We estimated the left ventricular diastolic function from the mitral inflow signal with Doppler. We determined the ratio of early peak flow velocity (*E*) to atrial peak flow velocity (*A*) (*E*/*A* ratio), and measured the isovolumic relaxation time, the acceleration and deceleration times, and the deceleration rate of the early diastolic flow [10, 25].

Radionuclide cineangiography. In total, 31 patients in group A, 25 patients in group A+XRT, 9 patients in group XRT and 26 control children, all appropriate for body size and age, were examined by radionuclide cineangiography, again by a single observer. ECG-gated radionuclide cineangiography was performed with the patient in the supine position at rest [17–19, 26]. Red blood cells were labelled *in vivo* with 2 mCi/10 kg of i.v. injected ^{99m}Technetium 20 min after i.v. administration of 0.3 mg/kg of stannous chloride. All studies were performed using an Elscint gamma camera interfaced with an Apex 415 ECT computer (Elscint, Haifa, Israel). In each study data were obtained with the patient at rest for 5 min. The left ventricular ejection fraction was measured [17, 18, 26]. The result was considered abnormal if the ejection fraction was below 50%. For diastolic function, the peak filling rate was used.

Chest X-rays taken at the time of the study were compared with those of the same patients taken before any treatment, and at discontinuation of therapy. Echocardiographic studies and radionuclide cineangiograms of the patients were compared with those of the control group, since earlier data were not available.

Risk factors

To examine the effects of different risk factors, we analysed the influence upon myocardial systolic and diastolic function of the cumulative dose of anthracyclines, the duration of follow-up after completion of anthracycline therapy, and the age at diagnosis, age at follow-up, dose of chest irradiation and sex.

Statistical methods

Analyses were performed by means of Macintosh StatView 512+ software. We used Student's *t*-test with two-tailed *P* values. Multivariance analysis was used to determine the effect of the different risk factors on myocardial function. Linear regression analysis was used to study the correlation between the cumulative dose of anthracyclines and the systolic indices of myocardial function.

RESULTS

Chest X-ray

The relative heart volume measurements at diagnosis, at discontinuation of therapy, and at follow-up all gave results within normal limits. No patient had a pathologically large cardiac volume at the time of the study, and none had pulmonary congestion. At the last follow-up, the heart volume was 330 ± 60 cm^3/cm^2 in group A, 280 ± 50 cm^3/m^2 in group A+XRT, and 310 ± 100 cm^3/m^2 in group XRT.

Echocardiography

In echocardiography, the mean ± S.D. left ventricular end-diastolic diameter, corrected for body surface area, was 42 ± 3 mm in group A ($P = 0.0001$), 40 ± 4 mm in group A+XRT (ns), 38 ± 5 mm in group XRT (ns), and 39 ± 3 mm in the control group. The mean ± S.D. thickness of the left ventricular posterior wall in end-diastole, corrected for body surface area, was 6 ± 1 mm in group A ($P = 0.0001$), 6 ± 1 mm in group A + XRT ($P = 0.0001$), 6 ± 1 mm in group XRT ($P = 0.01$) and 7 ± 1 mm in the control group. Left ventricular posterior wall thickness in end-diastole, plotted against body surface area, in controls and in patient groups is shown in Figure 1.

Our control subjects matched quite well with the material published by Colan and associates [23], with a mean score of the V_{cfc}-end-systolic wall stress ratio of 0.3 S.D., and the individual values were plotted reasonably well within ± 2 S.D. of Colan (Figure 2), particularly for the lower limit. The left ventricular contractility was abnormal (<–2 S.D. according to Colan's curves based on a normal population) in 17/53 (32%) group A patients, in 13/26 (50%) group A+XRT patients, and in 1/12 (8%) group XRT patients, and in 1 patient in our control group (Figure 2). In addition, although the majority of the individual values were within normal limits, the treatment groups differed significantly from the control group; the mean S.D.-score was 0.3 in the control group, –1.3 in group A ($P = 0.0001$), –2.0 in group A+XRT ($P = 0.0001$) and –1.1 in group XRT ($P = 0.005$). The difference between groups A and A+XRT was also significant ($P = 0.04$).

The LV wall stress was elevated, i.e. > 60 g/cm^2, in 13/53 (25%) patients in group A, in 2/26 (8%) patients in group

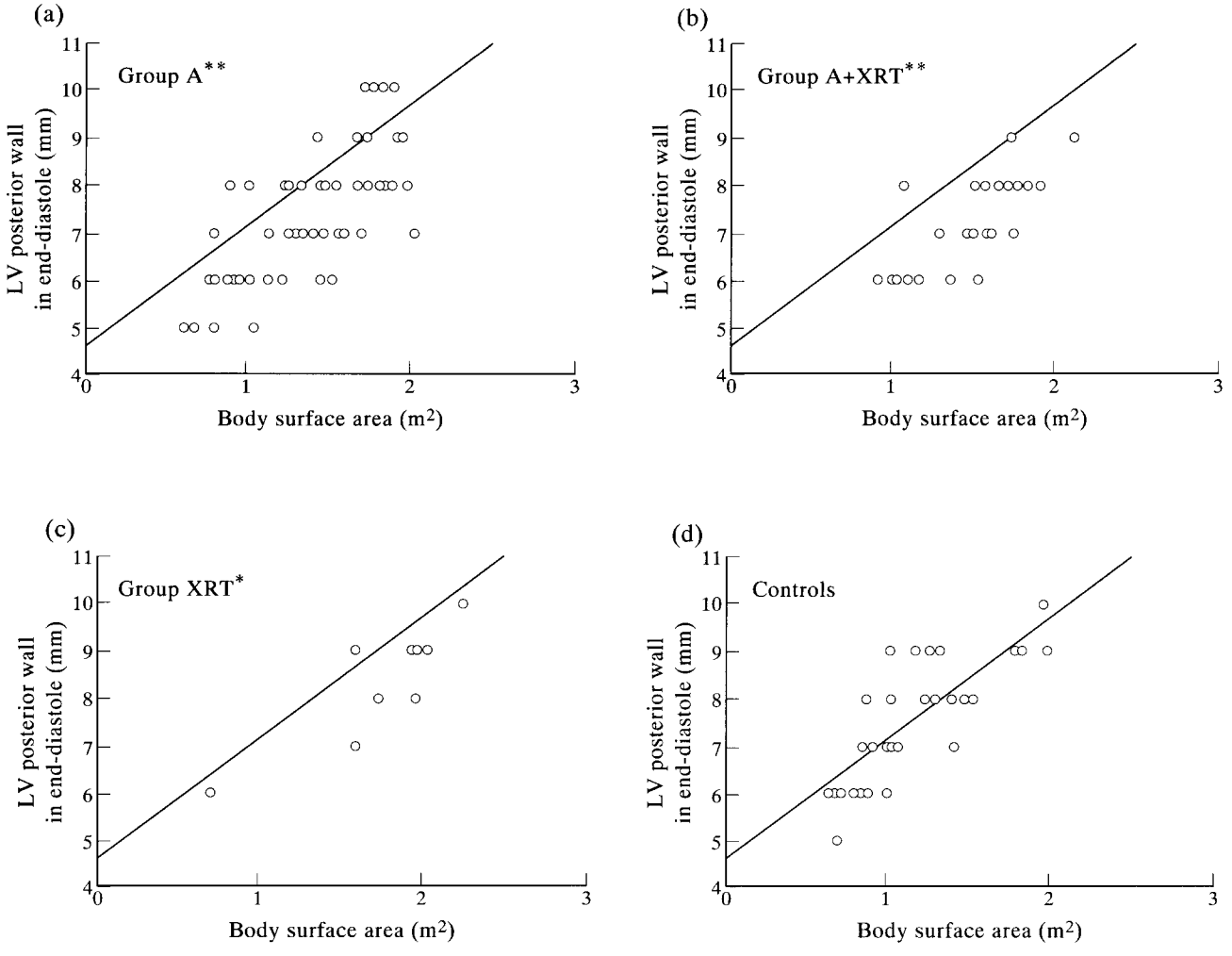

Figure 1. Thickness of the left ventricular posterior wall in end-diastole, plotted against body surface area, in controls and in different patient groups. The linear regression line of the control group ($r = 0.79$) is also shown for comparison of the patient groups. ** $P = 0.0001$, * $P = 0.01$, as compared with the control group.

A+XRT, and in 1/12 (8%) patient in group XRT and in 4/38 (11%) in the control group (Figure 2). The mean ± S.D. wall stress was 52 ± 12 g/cm² in group A ($P = 0.001$), 49 ± 10 g/cm² in group A+XRT (ns), 44 ± 10 g/cm² in group XRT (ns), and 44 ± 9 g/cm² in the control group.

Of the diastolic indices obtained from echocardiograms, the isovolumic relaxation time was significantly longer in group A ($P < 0.001$) than in the control group (Figure 3), the deceleration time of the early diastolic flow was significantly longer ($P < 0.001$ for groups A and A+XRT, $P < 0.01$ for group XRT), and the deceleration rate of the early diastolic flow was significantly slower ($P < 0.001$ for groups A and A+XRT, $P < 0.01$ for group XRT; Figure 3) in all treatment groups than in the control group. Other echocardiographic parameters of diastolic function were normal in every group, and no differences were observed between the groups.

Radionuclide cineangiography

The radionuclide LV ejection fraction correlated with the echocardiographic parameters, i.e. with fractional shortening ($P < 0.0001$), the V_{cfc}-end-systolic wall stress ratio ($P < 0.0001$) and end-systolic wall stress ($P < 0.02$).

In radionuclide cineangiography, the mean ± S.D. ejection fraction at rest was lower in all three study groups than in the control group: 56 ± 11% in group A ($P = 0.002$), 58 ± 10% in group A+XRT ($P = 0.005$), 60 ± 7% in group XRT (ns), and 65 ± 7% in the control group (Figure 4). The difference between groups A and A+XRT was not significant. An ejection fraction of less than 50% was observed in 6/31 (19%) group A patients, in 6/25 (24%) group A+XRT patients, in 1 patient (8%) in group XRT, but in none in the control group (Figure 4). In the radionuclide peak filling rate, no differences were observed between the treatment groups and the controls.

Risk factors

In multivariance analysis, the only factor significantly predicting decreased contractility was the cumulative dose of anthracyclines ($P < 0.05$). None of the other factors, such as duration of follow-up after completion of anthracycline therapy ($P = 0.32$), dose of irradiation ($P = 0.53$), age at diagnosis ($P = 0.06$), age at follow-up ($P = 0.14$) or sex ($P = 0.38$), proved to be a significant risk factor regarding contractility. Of the diastolic indices, increased deceleration time and decreased deceleration rate of the early diastolic flow were predicted by the cumulative dose of anthracyclines ($P < 0.005$) and the dose of irradiation ($P < 0.02$).

In linear regression analysis, the cumulative dose of anthracyclines correlated negatively with the radionuclide ejection

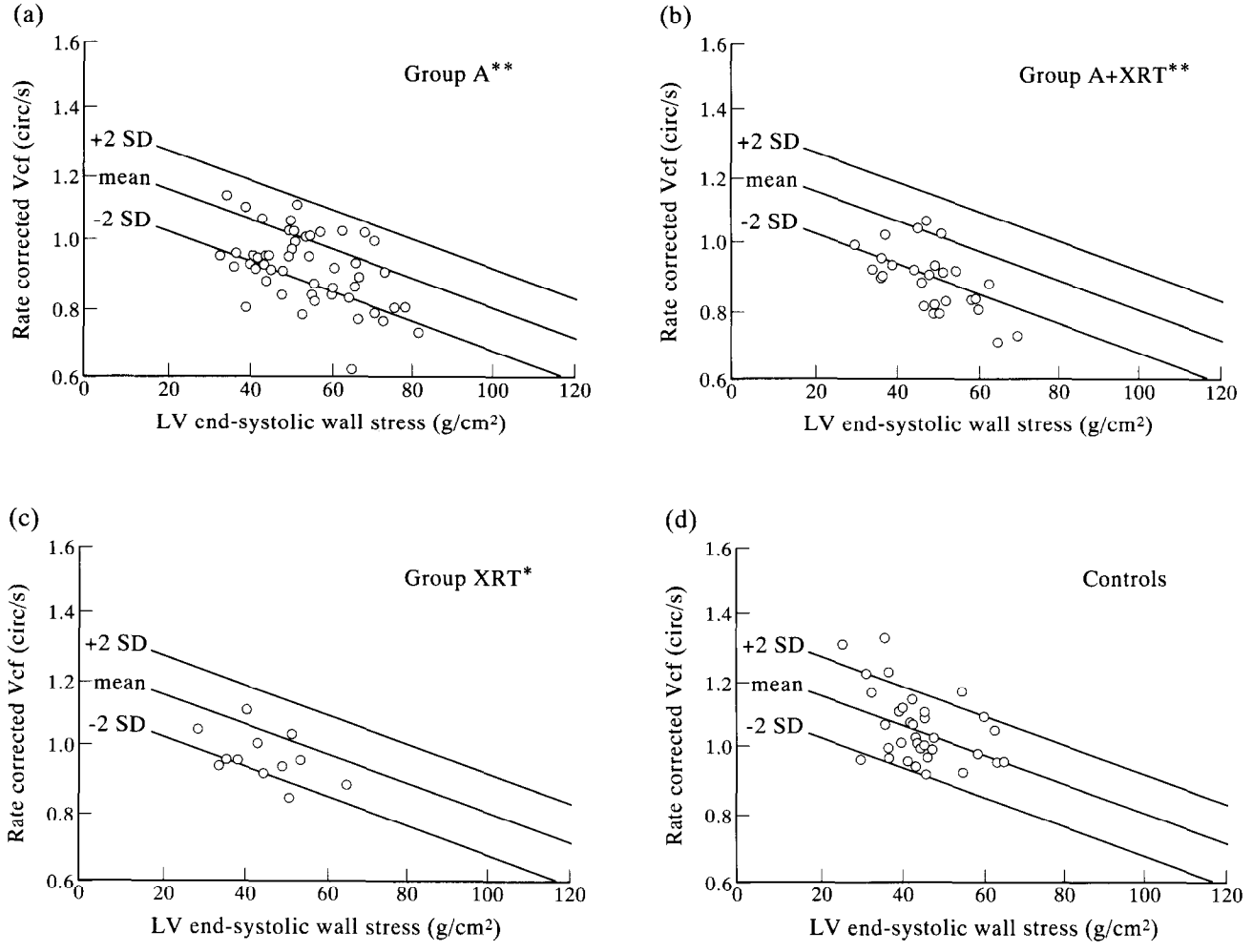

Figure 2. Left ventricular contractility in different patient groups and in the controls, expressed as rate-corrected velocity of fibre shortening (V_{cf}) plotted against end-systolic wall stress, using the curves published by Colan and associates [23]. ** $P = 0.0001$, * $P = 0.005$, as compared with the control group.

fraction ($P < 0.01$) (Figure 5) and the echocardiographic fractional shortening ($P < 0.003$), and positively with an increase in wall stress ($P < 0.03$).

DISCUSSION

Our patients, examined 1–12 years after treatment with anthracyclines and/or chest irradiation, were clinically asymptomatic, but had a high incidence of subnormal systolic and diastolic function. Deterioration of myocardial function was indicated by findings in echocardiography and radionuclide cineangiography. Most of the patients were still very young, and some had a relatively short follow-up.

Our results are in accordance with previous reports [8–10]. Lipshultz and coworkers detected abnormalities in either left ventricular contractility or wall stress in 57% of patients treated with anthracyclines [8]. Hausdorf and coworkers reported increased LV wall stress and impaired diastolic function in patients treated with anthracyclines [10]. Marchandise and coworkers found that LV diastolic function abnormalities precede systolic dysfunction [27].

Radiotherapy has been shown to increase the incidence of congestive heart failure after anthracycline therapy [1, 2]. Steinherz and coworkers reported an increased incidence of abnormalities in cardiac function in patients who, in addition to anthracycline therapy, had also received mediastinal irradiation [9]. In many anthracycline studies, patients treated with irradiation have been excluded [8, 10]. Conversely, in many studies reporting cardiac side-effects of irradiation, the patients have not received anthracyclines [13–15]. We therefore regarded it as important to examine the effect on myocardial function of anthracyclines and irradiation combined.

In our series, group A patients, with the highest cumulative dose of anthracyclines, differed from the untreated controls in both echocardiography and radionuclide cineangiography. The echocardiographic indices of systolic performance (S.D. score, FS) were lower, afterload/wall stress was higher (Figure 2), and the radionuclide ejection fraction was lower (Figure 4) than in the control group. Additionally, there were differences in diastolic function: the isovolumic relaxation time was longer and the deceleration rate of the early diastolic flow was slower (Figure 3) than in the control group. These changes indicate both systolic and diastolic dysfunction.

The contractility of the left ventricle was lowest in group A+XRT, as estimated from the V_{cfc}/end-systolic wall stress ratio (Figure 2). Similarly, although the median ejection fraction was not lowest by radionuclide cineangiography in group A+XRT, the incidence of abnormal findings in this group was highest (Figure 4). In group A+XRT, the cumulative dose

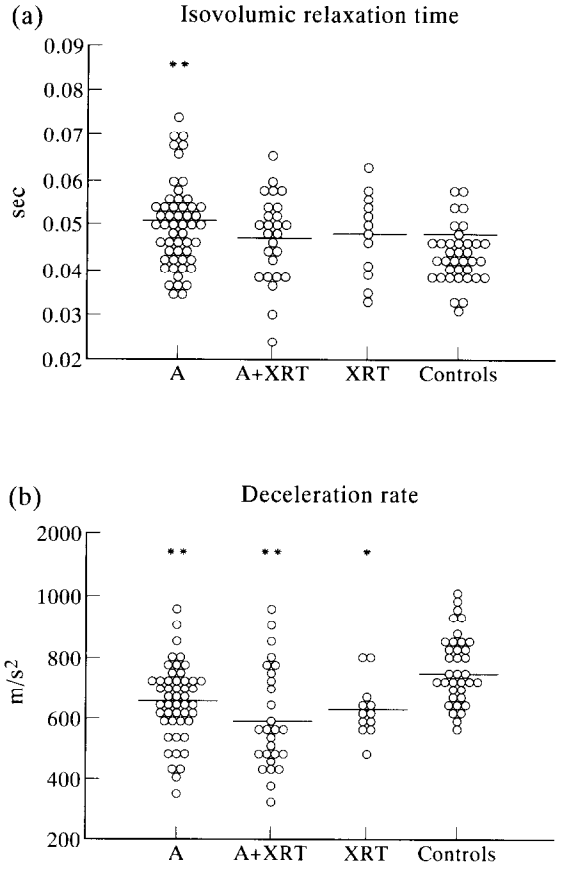

Figure 3. Isovolumic relaxation time and deceleration rate of early diastolic flow in patient groups and controls. Horizontal line, mean. ** $P < 0.001$, * $P < 0.01$ as compared with the control group.

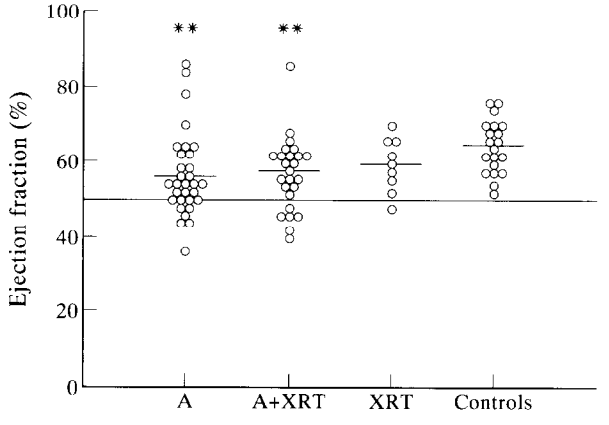

Figure 4. Radionuclide ejection fraction of left ventricle in the treatment groups and the controls. Horizontal line, mean. ** $P < 0.01$, as compared with the control group.

of anthracyclines was significantly lower than in group A, indicating that radiation therapy has an additive effect on anthracycline cardiotoxicity (Figures 2 and 4).

Group XRT seemed to have tolerated the therapy better than the anthracycline groups in terms of myocardial function. Left ventricular function, measured by radionuclide cineangiography was normal in all but 1 patient of this group. In echocardiography, only 1 patient had elevated wall stress and

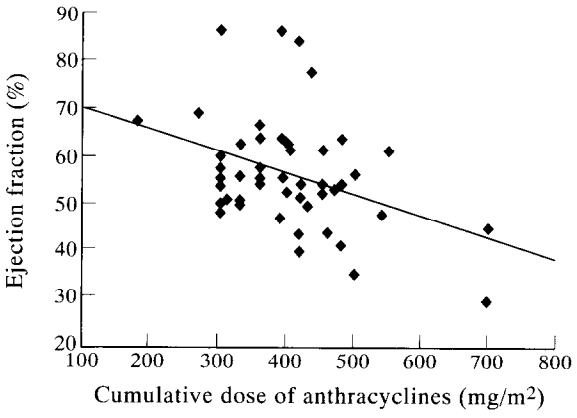

Figure 5. Correlation between the cumulative dose of anthracyclines and the ejection fraction in radionuclide cineangiography. Linear regression analysis with individual plots ($P < 0.01$).

another had decreased contractility (S.D. score below −2, Figure 2). Group XRT differed from the control group, however, in the echocardiographic S.D. score of contractility and in diastolic deceleration time and rate (Figure 3). Other parameters of systolic and diastolic function were normal. Irradiation produces inflammation of different tissues, and is associated more with an increased incidence of coronary artery disease and pericardial disease [11–13]. The young age of our patients and the follow-up time did not allow evaluation of premature coronary artery disease.

Anthracycline cardiomyopathy may appear or progress years after completion of therapy [8, 9, 28]. Anthracycline therapy and chest irradiation may lead to loss of myocytes, the result being a progressive decrease in the left ventricular mass. In children, this may lead to inadequate increase in the left ventricular mass as the child grows [8]. Accordingly, in our series, in the treatment groups A, A+XRT and XRT, the left ventricular posterior wall was thinner than in the control group, suggesting loss of myocytes (Figure 1).

In multivariance analysis, the cumulative dose of anthracyclines was a significant risk factor for reduced contractility or increased wall stress. The age of the patients, previously shown to be a risk factor for increased wall stress [8], did not reach statistical significance in our study. The cardiotoxicity from radiotherapy [15] as well as anthracycline cardiotoxicity [9] have been shown to increase with time. In our study, the median follow-up of 4 years may not have been long enough to confirm this finding. The dose of irradiation and the cumulative dose of anthracyclines proved to be risk factors for diastolic dysfunction as evidenced by decreased deceleration rate and prolonged deceleration time of the early diastolic flow.

Tolerance of anthracyclines is individual, and no absolute safety limits can be set for the cumulative dosage [29]. The previously recommended dose limit of 500 mg/m² of anthracyclines seems to be associated with an alarmingly large number of abnormal cardiac findings. It should be taken into account that the myocardial damage caused by anthracyclines and chest irradiation is additive. Accordingly, patients receiving additional irradiation in the heart area are probably at higher risk of developing myocardial damage.

Radionuclide ejection fraction correlated with echocardiographic measures of contractility and confirmed them. With

these methods, it is possible to detect latent myocardial damage in yet asymptomatic patients. These measures also correlate with myocardial histological changes [17, 19, 30]. Regarding radionuclide cineangiography, there is some concern about the radiation exposure, especially in repeated examinations. Therefore, echocardiography has been primarily recommended for clinical follow-up, and radionuclide cineangiography may be used as an additive or confirmatory method [29]. Chest X-rays were normal in all children, although the contractility of the left ventricle was impaired in a large proportion of patients. Accordingly, chest X-ray is of no value in detecting anthracycline cardiomyopathy, and may even be misleading if used alone in the follow-up.

We conclude that a significant proportion of children and adolescents treated with anthracyclines and/or chest irradiation experience cardiotoxicity. In most cases, this cardiotoxicity seems to be subclinical and mild. Because very long-term follow-up data is limited, patients recciving these therapies, especially growing children, need to be closely monitored for years after completed anticancer therapy [29].

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