

Long term doxorubicin cardiotoxicity in childhood: non-invasive evaluation of the contractile state and diastolic filling

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SUMMARY Cardiac performance was evaluated at least two years after doxorubicin treatment in childhood in 55 patients without overt congestive cardiomyopathy. None of the patients had received mediastinal irradiation. Computer-assisted analysis of digitised echocardiograms showed impaired rapid diastolic filling and an increased change of dimension between minimal cavity dimension and mitral valve opening. This impairment of diastolic function was related to the cumulative dose of doxorubicin. In contrast when angiotensin II was infused to increase the afterload the end systolic pressure-length and stress-shortening relation indicated normal left ventricular systolic function. But during baseline conditions the end systolic wall stress was significantly increased in patients in whom the cumulative dose of doxorubicin exceeded 360 mg/m².

Doxorubicin is a highly effective antineoplastic agent, but its use is limited by a cumulative dose-related cardiomyopathy.¹ There is still considerable concern about long term cardiac performance after antineoplastic treatment with doxorubicin, particularly in childhood.²⁻⁴ The cumulative dose of doxorubicin should be limited to 450 mg/m² body surface area.¹ But some patients develop cardiomyopathy even at lower cumulative doses, particularly when there are additional risk factors such as mediastinal irradiation.¹ Doxorubicin can cause specific ultrastructural changes in the myocardium at much lower cumulative doses, without altering left ventricular function.⁵⁻⁷ This suggests that even relatively low cumulative doses of doxorubicin can cause subclinical damage.

The standard indices of left ventricular performance—the ejection phase indices—cannot discriminate between abnormal contractility and altered loading conditions (preload and afterload).⁸⁻¹⁰ Although the extent of myocardial fibre shortening is often used as an index of contractility, it is really a reflection of the interaction between contractile state,

preload, and afterload.⁹⁻¹¹ The slope of the end systolic pressure-length relation, however, is an index of the contractile state that is independent of load.¹²⁻¹⁴ The end systolic stress-shortening relations seem to be even more sensitive measures of impaired contractility.⁹⁻¹¹

Chronic anthracycline cardiotoxicity can alter diastolic function too. Recently Mortensen *et al* reported haemodynamic and structural findings suggestive of restrictive endomyocardial disease after treatment with anthracyclines.¹⁵ Altered diastolic properties were also recognised by computer-assisted analyses of digitised echocardiograms.^{16 17} These reports show that diastolic function must be studied when the effect of chronic doxorubicin cardiotoxicity is being examined.

We evaluated long term cardiac performance after doxorubicin treatment in childhood. We studied the contractile state by analysing the end systolic pressure-length and stress-shortening relations and we used computer-assisted analysis of digitised echocardiograms to evaluate diastolic filling.

Patients and methods

PATIENT GROUP

We studied 55 patients who had been treated with doxorubicin for childhood malignancies. In all

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patients doxorubicin was part of a multiple drug regimen (*leukaemia*: doxorubicin, vincristine, methylprednisolone, cyclophosphamide, 6-mercaptopurine, arabinoside-C; *osteosarcoma*: doxorubicin, methotrexate, bleomycin, actinomycin-D, cyclophosphamide; *Ewing's sarcoma and soft tissue sarcoma*: doxorubicin, vincristine, cyclophosphamide, actinomycin-D, bleomycin).

All patients were in complete remission after the end of antineoplastic treatment. None of them had been treated by irradiation of the mediastinum. The cumulative dose of doxorubicin ranged from 31 to 656 mg/m² (mean (SD) 273 (152) mg/m²). All patients had been off treatment for at least two years (range 2.1 to 10.4). We selected those who had been off treatment for the longest time from among patients who had had similar cumulative doses of doxorubicin. After five patients had been excluded from the study (see Results) patients were arbitrarily divided into three groups according to their cumulative dose of doxorubicin: *group 1* (n=20), <180 mg/m²; *group 2* (n=13), 180–360 mg/m²; *group 3* (n=17), >360 mg/m².

CONTROL GROUP

The control group consisted of 30 healthy volunteers aged 18–30.⁸ None had a history of cardiovascular disease. Physical examination, electrocardiography, M mode echocardiography, and cross sectional echocardiography showed no abnormalities. None of them was taking medications.

ECHOCARDIOGRAMS

Echocardiograms were performed with Picker 80C Echoview ultrasound imaging device with a 3.5 MHz and 2.25 MHz transducer. The M mode echocardiograms were recorded at the tip of the mitral valve leaflets in the standard position at a paper speed of 100 mm/s.¹⁸ The transducer was held in position for all measurements. All echocardiograms were recorded by one echocardiographer to eliminate interobserver variability. A carotid pulse tracing was recorded simultaneously with the M mode echocardiogram. It was corrected for pulse transmission delay by aligning it with the aortic valve echocardiogram.

EVALUATION OF THE CONTRACTILE STATE

Measurement of end systolic pressure

Systolic and diastolic blood pressure were measured by a Dinamap 845 Vital Signs Monitor (Criticon Inc.). This device has been shown to estimate central aortic pressure accurately over a wide range of pressure and independently of cardiac index, systemic vascular resistance, heart rate, and body surface area.¹⁹ The end systolic pressure (P_{es}) was

estimated by the method of Stefadourous *et al*²⁰ by linear interpolation of the height of the dicrotic notch of the indirect carotid pulse tracing.^{19,20}

Study protocol

All examinations were performed in patients resting in the semisupine position. The patients relaxed for at least 10 minutes before the examination. Intravenous atropine (0.01 mg/kg) was given before the examination, to reduce reflex cardiac slowing.⁸ After baseline recordings the blood pressure was slowly increased by the infusion of angiotensin II (0.5–3.5 µg/min). We attempted to increase systolic blood pressure to 30 mm Hg above baseline values. During the increase in blood pressure we made several simultaneous recordings of the M mode echocardiogram, carotid pulse tracing, and arterial blood pressure. We obtained the informed consent of all patients or their parents. The study protocol was approved by the local committee for human research.

Measurements and calculation

We took the mean of three consecutive cardiac cycles. Data points were excluded when the heart rate varied by more than 10 beats per minute from baseline values.^{8–10} The end diastolic internal left ventricular dimension (D_{ed}) was measured at the start of the QRS complex of the electrocardiogram and the end systolic left ventricular dimension (D_{es}) and posterior wall thickness (PW_{es}) were measured at end ejection (assessed from the time corrected carotid pulse tracings). Ejection time (ET) was measured from the carotid pulse tracing. The end diastolic left ventricular dimension was corrected for differences of body surface area (BSA) according to²¹:

$$D_{ed(\text{corr})} = D_{ed} \times (BSA)^{-1/3}.$$

Fractional shortening (FS) was calculated as:

$$FS = \frac{D_{ed} - D_{es}}{D_{ed}} \times 100\%.$$

Mean fibre shortening velocity (VCF_{mean}) as:

$$VCF_{\text{mean}} = (FS/ET) \times 10 \text{ s}^{-1}.$$

End systolic meridional wall stress (σ_{es}) was calculated according to the method of Brodie *et al*²²:

$$\sigma_{es} = 1.35 \times \frac{PW_{es} \times D_{es}}{4 \times PW_{es} \times (1 + PW_{es}/D_{es})} \text{ (g/cm}^2\text{)}.$$

The slopes a_1 to a_3 of the relations between end systolic pressure and dimension ($P_{es} - D_{es}$ relation), end systolic wall stress and fractional shortening ($\sigma_{es} - FS$ relation), and end systolic wall stress and mean fibre shortening velocity ($\sigma_{es} - VCF$ relation) were calculated according to the following equations:
 $P_{es} - D_{es}$ relation: $P_{es} = a_1 \times D_{es} + b$
 $\sigma_{es} - FS$ relation: $FS = a_2 \times \sigma_{es} + b$
 $\sigma_{es} - VCF$ relation: $VCF = a_3 \times \sigma_{es} + b$

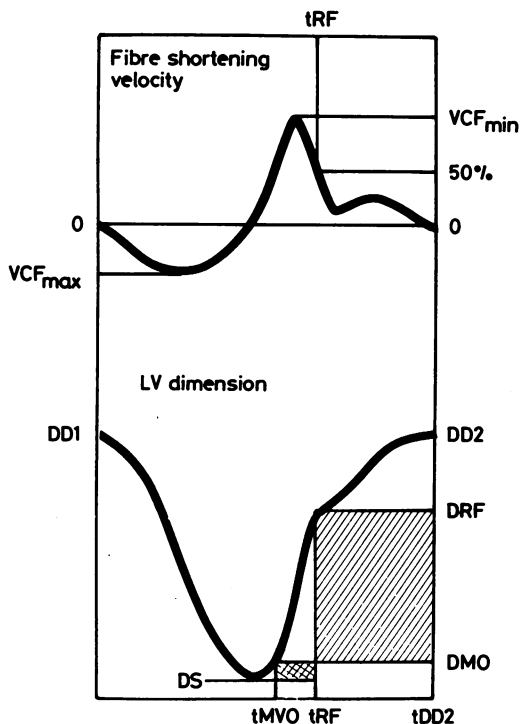


Fig 1 The instantaneous left ventricular (LV) internal dimension (lower curve) and its first derivative, the fibre shortening velocity (upper curve). DD1, end diastolic dimension at the beginning of the cardiac cycle; DD2, end diastolic dimension at the end of the cardiac cycle; DS, minimal left ventricular dimension; DMO, dimension at mitral valve opening; DRF, dimension at the end of rapid diastolic filling (point at which the normalised fibre shortening velocity had decreased to 50% of its peak value); tMO, time of mitral valve opening; tRF, time of the end of rapid diastolic filling; tDD2, end of cardiac cycle; VCF_{max}, maximal fibre shortening velocity; VCF_{min}, minimal fibre shortening velocity or maximal fibre lengthening rate.

EVALUATION OF DIASTOLIC FUNCTION

Computed-assisted analyses

We used only good quality echocardiograms for computer-assisted analysis. The M mode echocardiograms were manually digitised with a Cardio 200 computer (Kontron Image Analysis). Three consecutive cardiac cycles were analysed and the mean was used for further calculations. The following were measured:

Measurement of time intervals—Time intervals were measured from the beginning of the Q wave. The interval between minimal cavity dimension and mitral valve opening (tDS-MO) was measured from the point at which the fibre shortening velocity curve crossed zero to the time of mitral leaflet separation (fig 1).^{23,24}

Measurement of dimensions and changes in dimen-

sion—The end diastolic left ventricular dimension (DD) was measured at the beginning of the first Q wave of the cardiac cycle being analysed. Left ventricular dimension at aortic valve closure was taken as the end systolic dimension (D_{es}). The maximal normalised fibre lengthening rate (VLR_{max}) was measured as the maximum of the first derivative of the left ventricular internal dimension curve that was standardised according to the instantaneous left ventricular dimension.²³ Minimal cavity dimension (DS) was measured at the point where the first derivative of the instantaneous left ventricular dimension curve crossed zero.

The change of dimension between minimal cavity dimension and mitral valve opening was defined as^{23,24}:

$$dDS - MO = \frac{DMO - DS}{DD2 - DS} \times 100\%$$

where DMO is the dimension at mitral valve opening; DS, minimal cavity dimension; and DD2, end diastolic dimension at the end of the cardiac cycle.

The end of rapid diastolic filling was defined as that point where the fibre shortening velocity had decreased to 50% of its peak value (fig 1).²⁵ The change of dimension with rapid diastolic filling (dRF) was calculated as:

$$dRF = \frac{DRF - DMO}{DD2 - DMO} \times 100\%$$

where DRF is the dimension at the end of rapid diastolic filling; DS, minimal cavity dimension; DMO, dimension at mitral valve opening; and DD2 end diastolic dimension at the end of the cardiac cycle.

STATISTICAL ANALYSIS

Linear regression analysis was performed to calculate the slope values of the individual relations between end systolic pressure and dimension, end systolic wall stress and fractional shortening, and end systolic wall stress and mean velocity of fibre shortening. At least five data points were available in all patients and controls. The three patient groups and the control group were compared by analysis of variance with the SAS-program and the differences between two groups were tested by Duncan's multiple range test.

To eliminate the influence of different ages (and so differences of body surface area and heart rate) and different time intervals between end of treatment and investigation, analysis of covariance was performed with the covariates "age at investigation" and "time interval between end of treatment and investigation"; differences between the adjusted means were tested by a t test matrix. A p value of <0.05 was regarded as statistically significant.

Table 1 Mean (SD) baseline haemodynamic function

	Group 1	Group 2	Group 3	Control
Heart rate (beats/min)	81 (16)	76 (19)	74 (17)	63 (10)
D _{ed} (mm)	44 (4.4)	48 (7.6)	48 (5.5)	48 (3.5)
D _{ed (corr)}	40 (2.5)	40 (4.9)	40 (3.8)	40 (2.2)
P _{sys} (mm Hg)	116 (11)	125 (15)	117 (9)	121 (7)
P _{es} (mm Hg)	84 (12)	92 (18)	85 (11)	89 (9)
σ _{es} (g/cm ²)	49 (11)	56 (28)	59 (21)	50 (10)
FS (%)	34 (4.3)	34 (6.5)	31 (5.2)	34 (2.6)
VCF _{mean} (cm/s)	1.2 (0.20)	1.2 (0.24)	1.1 (0.19)	1.1 (0.12)

D_{ed}, end diastolic dimension; D_{ed (corr)}, end diastolic dimension corrected for differences in body surface area; P_{sys}, systolic arterial blood pressure; P_{es}, end systolic pressure; σ_{es}, end systolic meridional wall stress; FS, fractional shortening; VCF_{mean}, mean fibre shortening velocity.

Results

PATIENT DATA

The mean (SD) age at the time of investigation was 16.7 (5.4) and the age at the end of antineoplastic treatment was 12.1 (4.9). The mean (SD) cumulative dose of doxorubicin was 273 (152) mg/m² (range 31–656 mg/m²) (group 1, 120 (42) mg/m² (31–180 mg/m²); group 2, 278 (74) (182–355 mg/m²); group 3, 450 (70) mg/m² (363–656 mg/m²). Five patients of the 55 patients had to be excluded from the study: one patient had an overt cardiomyopathy, two patients had raised blood pressure (in these three patients afterload challenge was not performed), and two patients had technically unsatisfactory echocardiograms.

BASELINE HAEMODYNAMIC FUNCTION

Table 1 shows the haemodynamic data at baseline conditions and table 2 shows the adjusted means

according to analyses of covariance. Heart rates were significantly different in the various groups (analysis of variance $p < 0.01$), but after adjustment of the means for the age at investigation, analysis of covariance showed no difference (table 2). The end diastolic left ventricular dimension was significantly different in the various groups (analysis of variance $p < 0.03$); again, this was because of the age at the time of investigation (table 2) and the associated differences of the body surface area. After correction for body surface area (D_{ed (corr)}) the end systolic dimension was similar in all the groups (table 1).

The end systolic wall stress was significantly higher in patients with a cumulative dose of doxorubicin of > 360 mg/m² (analysis of covariance $p < 0.03$), whereas systolic, diastolic, mean, and end systolic arterial blood pressure were not significantly different in the various groups. No significant differences of fractional shortening and mean fibre shortening velocity were seen between the groups.

Table 2 Baseline haemodynamic function (mean (SD)) with means adjusted for age at investigation and time since the end of antineoplastic treatment according to analysis of covariance

	Group 1	Group 2	Group 3	Control
Heart rate (beats/min)	77 (3.7)	79 (4.3)	78 (4.0)	64 (8.0)
D _{ed}	45 (1.1)	46 (1.3)	47 (1.2)	48 (0.5)
σ _{es}	48 (3.6)	46 (4.3)	60 (3.9)	47 (5.9)
FS	34 (1.1)	36 (1.2)	31 (1.1)	34 (1.8)
VCF _{mean}	1.2 (0.04)	1.3 (0.05)	1.1 (0.05)	1.1 (0.10)

See footnote to table 1 for abbreviations.

Table 3 Indices (mean (SD)) of left ventricular systolic performance

	Group 1	Group 2	Group 3	Control
P _{es} - D _{es}	72.9 (24.9)	53.2 (19.9)	60.5 (23.1)	54.1 (18.4)
σ _{es} - FS	-0.204 (0.05)	-0.258 (0.05)	-0.216 (0.06)	-0.229 (0.04)
σ _{es} - VCF	-0.57 (0.27)	-0.84 (0.24)	-0.67 (0.26)	-0.66 (0.14)
<i>Means adjusted for age at investigation and time since end of antineoplastic treatment according to analysis of covariance</i>				
P _{es} - D _{es}	62.2 (5.4)	45.3 (4.9)	51.3 (5.3)	
σ _{es} - FS	-0.208 (0.014)	-0.257 (0.016)	-0.212 (0.015)	
σ _{es} - VCF	-0.62 (0.06)	-0.83 (0.07)	-0.62 (0.06)	

P_{es} - D_{es}, slope of the relation between end systolic left ventricular dimension and end systolic pressure; σ_{es} - FS, slope of the relation between end systolic wall stress and fractional shortening; σ_{es} - VCF, slope of the relation between end systolic wall stress and mean velocity of fibre shortening.

Table 4 Indices (mean (SD)) of left ventricular diastolic function

	Group 1	Group 2	Group 3	Control
dDS-MO (%)	4.7 (3.3)	10.8 (8.9)	16.7 (10.1)	7.4 (6.2)
dRF (%)	66.5 (13.7)	58.6 (17.5)	51.7 (18.9)	62.3 (6.2)
tDS-MO (ms)	42.1 (34.7)	58.5 (24.1)	66.5 (32.4)	34.9 (21.9)
VLR _{max} (s ⁻¹)	3.86 (1.06)	3.46 (0.95)	3.03 (0.92)	4.10 (1.23)

dDS-MO, change of dimension between minimal cavity dimension and mitral valve opening; dRF, change of dimension with rapid diastolic filling; tDS-MO, time between minimal cavity dimension and mitral valve opening; VLR_{max}, maximal normalised fibre lengthening rate.

LEFT VENTRICULAR SYSTOLIC PERFORMANCE

The relations between end systolic pressure and dimension, end systolic wall stress and fractional shortening, and end systolic wall stress and mean fibre shortening velocity were linearly related in the normal subjects and patients, with linear regression coefficients ranging from 0.883 to 0.998. The slopes for these relations were not significantly different in the patient groups and the control group (table 3).

LEFT VENTRICULAR DIASTOLIC FUNCTION

The change of dimension in the interval between minimal dimension and mitral valve opening (dDS-MO) differed significantly between the groups (table 4) (analysis of variance $p < 0.0001$, analysis of covariance $p < 0.0004$). It was significantly related to the cumulative dose of doxorubicin ($r = 0.488$). Similarly, the change of dimension with rapid diastolic filling (dRF) differed significantly between the groups (table 4) (analysis of variance $p < 0.04$, analysis of covariance $p < 0.01$) and was inversely related to the cumulative dose of doxorubicin ($r = -0.425$). It changed less in patients with a cumulative dose of doxorubicin > 360 mg/m² than in patients with a cumulative doxorubicin dose < 180 mg/m² ($p < 0.003$). The time between minimal cavity dimension and mitral valve opening was slightly longer in patients with a cumulative dose of doxorubicin > 360 mg/m² than in patients with a cumulative dose of doxorubicin < 180 mg/m², but neither analysis of variance nor analysis of covariance showed significant differences between the groups (table 4). The maximal normalised fibre lengthening rate was similar in all the groups.

Discussion

Little is known about the long term changes of cardiac function after doxorubicin treatment.²⁶ Because of the long life expectancy after successful antineoplastic treatment in childhood, evaluation of long term doxorubicin cardiotoxicity is important in this age group.^{1-4,27}

Endomyocardial biopsy has become the reference standard for monitoring doxorubicin cardiotoxicity; none the less, histological grading has been shown to correlate poorly with left ventricular performance in

most studies.^{6,7,28} Left ventricular performance seems to be a more important indicator of toxicity than the histological appearance of the right ventricular myocardium. None of the patients we studied had received mediastinal irradiation or had overt cardiomyopathy.

DIASTOLIC FUNCTION AFTER DOXORUBICIN TREATMENT

Most studies of doxorubicin cardiotoxicity have focused on impaired left ventricular ejection. But diastolic function seems to be at least as important.¹⁵⁻¹⁷ We found that diastolic filling was significantly impaired after doxorubicin treatment in childhood. This impairment was related to the cumulative dose of doxorubicin (table 4) and was characterised by an impairment of rapid diastolic filling and an increased change of dimension between minimal cavity dimension and mitral valve opening.

In contrast with the isovolumic relaxation period, that is the interval between aortic valve closure and mitral valve opening, the interval between minimal cavity dimension and mitral valve opening (tDS-MO) was independent of the timing of aortic valve closure and reflected the timing of mitral valve opening. The change of dimension in this period is usually small.^{23,24} An increase in the change of dimension between minimal cavity dimension and mitral valve opening reflects increased changes of left ventricular shape before mitral valve opening—that is incoordinate relaxation and impaired early diastolic function. Similarly, reduced early diastolic filling reflects impaired early diastolic function.

These alterations of diastolic filling could reflect restrictive endomyocardial disease,^{29,30} as reported by Mortensen *et al.*¹⁵ Others have reported echocardiographic evidence of altered diastolic properties during antineoplastic treatment.^{16,17} Our data indicate that impaired early diastolic function can persist at least for some years after the end of treatment.

CONTRACTILE STATE AFTER DOXORUBICIN TREATMENT

Recently, the slope of the end systolic pressure-length relation has been shown to be a load-independent and sensitive index of doxorubicin cardiotox-

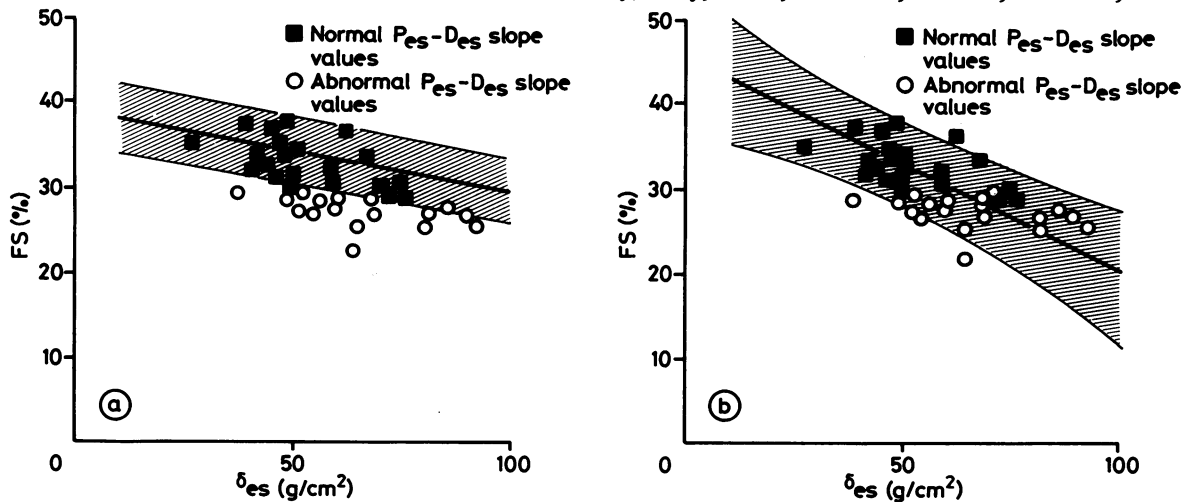


Fig 2 (a) Individual baseline values for end systolic wall stress and fractional shortening from a study by Borow *et al*¹⁰ and the normal range for the relation between end systolic wall stress (σ_{es}) and fractional shortening (FS) as defined by a afterload increase produced by methoxamine in normal subjects.¹⁰ The open circles are patients with an abnormal end systolic pressure-length relation ($P_{es}-D_{es}$). (b) The same data points together with the normal range as defined by a afterload increase produced by angiotensin II.⁸ Most of the baseline stress-shortening data outside the normal range as defined by afterload increase with methoxamine are within the normal range as defined by angiotensin II.

icity.¹⁰ The end systolic stress shortening relations seem to be a more sensitive index than the pressure-length relation.^{9,10} The end systolic stress-shortening relations reflect the interaction of forces working on the left ventricle at end ejection and the extent of fibre shortening.^{9,10}

We found that doxorubicin treatment in childhood had no effect on end systolic pressure-length and stress-shortening relations 2.1–10.4 years later. Surprisingly the contractile state was slightly increased in patients with a cumulative doxorubicin dose < 180 mg/m². This could be the result of increased sympathetic drive because unlike the normal subjects these patients knew that they were being investigated for possible heart disease.

End systolic wall stress during baseline conditions was significantly increased in patients in whom the cumulative dose of doxorubicin was > 360 mg/m². This increase reflects an increased afterload³¹ (tables 1 and 2). This result accords with the data reported by Borow *et al*, who showed that the baseline values of end systolic wall stress and fractional shortening predicted the contractile state after doxorubicin treatment¹⁰ (fig 2). But unlike these workers we increased afterload with angiotensin II⁸ not methoxamine¹⁰; this resulted in a different normal range with steeper gradients for the end systolic pressure-length and stress-shortening relations.⁸ Angiotensin II has negligible effects on preload, unlike methoxamine, and this difference may have influenced the end systolic pressure-length and stress-shortening relations in these two studies.

Most baseline data for stress-shortening relations that were outside the normal range after the afterload was increased with methoxamine (fig 2a) were within the normal range for studies in which the afterload was increased by angiotensin II in normal subjects (fig 2).^{8,10} Although it is normal for systolic emptying to be reduced and end systolic wall stress to be increased when the afterload is increased,³¹ a significant increase in end systolic wall stress during baseline conditions is definitely abnormal. So the measurement of the end systolic wall stress during baseline conditions may be an important method of monitoring doxorubicin cardiotoxicity.

Our data show that diastolic function is significantly altered after doxorubicin treatment in childhood. Impaired diastolic function was seen in patients without overt cardiomyopathy and was related to the cumulative dose of doxorubicin. It may be that impairment of left ventricular diastolic function is related to restrictive endomyocardial disease. We did not, however, find that the contractile state was significantly impaired (that is, doxorubicin had no effect on the end systolic pressure-length and stress-shortening relations). None the less, a significant increase of the end systolic wall stress during baseline conditions in patients with high cumulative doxorubicin dose showed that the afterload was increased after doxorubicin treatment in childhood.

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