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Prolongation of Isovolumetric Relaxation Time as Assessed by Doppler Echocardiography Predicts Doxorubicin-Induced Systolic Dysfunction in Humans

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A reasonably sensitive and specific noninvasive test for doxorubicin cardiotoxicity is needed. In addition, few data exist on the short- and long-term effects of doxorubicin on diastolic filling. To determine if pulsed Doppler indexes of diastolic filling could predict doxorubicin-induced systolic dysfunction, 26 patients (mean age 48 ± 12 years) were prospectively studied before receiving chemotherapy (control) and 3 weeks after obtaining cumulative doses of doxorubicin.

In nine patients developing doxorubicin-induced systolic dysfunction (that is, a decrease in ejection fraction by ≥10 ejection fraction units to <55%), the isovolumetric relaxation time was prolonged (from 65 ± 18 to 84 ± 24 ms, $p < 0.05$) after a cumulative doxorubicin dose of 100 to 120 mg/m^2. This prolongation preceded a significant decrease in ejection fraction. Other Doppler indexes of filling were impaired after doxorubicin therapy but occurred simultaneously with the decrease in ejection fraction.

A >37% increase in isovolumetric relaxation time was 78% (7 of 9) sensitive and 88% (15 of 17) specific for predicting the ultimate development of doxorubicin-induced systolic dysfunction. In 15 patients studied 1 h after the first treatment, doxorubicin enhanced Doppler indexes of filling and shortened isovolumetric relaxation time. In 22 patients, indexes of filling remained impaired and isovolumetric relaxation time was prolonged 3 months after the last doxorubicin dose.

In conclusion, doxorubicin-induced systolic dysfunction is reliably predicted by prolongation of Doppler-derived isovolumetric relaxation time. Early after administration, doxorubicin enhances filling and isovolumetric relaxation time. The adverse effects of doxorubicin on both variables persist at least 3 months after cessation of treatment.

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Doxorubicin has proved to be an effective antineoplastic agent in the treatment of malignant lymphoma, leukemia and several solid tumors (1–3). Unfortunately, serious and potentially irreversible dose-related cardiotoxicity may occur with its administration (4,5). Congestive heart failure develops in >30% of patients receiving >550 mg/m^2 of doxorubicin and may occur with lesser doses (4–7). Thus, achieving a cumulative dose of doxorubicin that is maximally efficacious with an acceptable degree of cardiotoxicity remains one of the most difficult dilemmas faced by the oncologist and cardiologist.

Several noninvasive techniques such as electrocardiography, phonocardiography and M-mode echocardiography are insensitive and nonspecific in monitoring doxorubicin-induced cardiotoxicity (8–10). Endomyocardial biopsy has been useful in guiding doxorubicin therapy, but it is an invasive procedure with associated risks and complications (8,10–12). Left ventricular ejection fraction at rest is used by many oncologists to guide doxorubicin therapy (13–15). However, mild heart failure may not be well predicted by ejection fraction at rest (13). Although a decrease in ejection fraction with exercise may improve the sensitivity of radionuclide angiography, stress testing has not gained popularity because many patients with a malignant neoplasm are debilitated and incapable of exercising. Thus, it is not certain which noninvasive studies are most useful in the early detection of doxorubicin cardiotoxicity or in guiding the maximally tolerable dose of doxorubicin for a given patient.

Numerous studies have examined the effect of doxorubicin on systolic function and it has been shown (16) that doxorubicin can cause endomyocardial fibrosis and result in impaired diastolic function as manifested by restrictive physiology. Some recent work (17,18) has suggested that diastolic filling abnormalities may precede systolic dysfunction in patients receiving doxorubicin. However, it is unknown whether impaired systolic function due to doxorubicin can be reliably predicted by any noninvasive index of diastolic filling. In addition, few data exist on the short- and potentially long-term effect of doxorubicin on diastolic filling (19). Thus, the goals of the present study were to determine the

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short- and long-term effect of doxorubicin on diastolic filling and the ability of pulsed Doppler indexes of diastolic function to predict doxorubicin-induced systolic dysfunction.

Methods

Study patients. Thirty-four patients scheduled to begin chemotherapy with doxorubicin in an anticipated cumulative dose of ≥200 mg/m^2 for any malignant neoplasm were enrolled in the study. Inclusion criteria included age ≥18 years, normal sinus rhythm and no prior treatment with any anthracycline derivative (for example, doxorubicin and daunomycin). Exclusion criteria included chest irradiation therapy between the first dose and up to 3 weeks after the last dose of doxorubicin, left ventricular ejection fraction <55% before therapy, more than mild aortic or mitral regurgitation as assessed by pulsed and Doppler color flow echocardiography (20–23), aortic or mitral valve stenosis (24,25), a prior history of cardiac disease or congestive heart failure, suspected coronary artery disease (that is, a history of angina or myocardial infarction, abnormal findings on a 12-lead electrocardiogram (ECG) or segmental or global wall motion abnormality on two-dimensional echocardiography), failure to achieve a cumulative doxorubicin dose of ≥200 mg/m^2 for reasons unrelated to cardiotoxicity and a technically inadequate two-dimensional or Doppler echocardiogram. Eight patients were excluded for the following reasons: a technically inadequate echocardiogram (n = 3), a cumulative doxorubicin dose <200 mg/m^2 (n = 4) and an ejection fraction <55% before therapy (n = 1). Thus, the study group consisted of 26 patients (22 women and 4 men) with a mean age of 48 ± 12 years (range 20 to 69) being treated for breast carcinoma (n = 19), lung carcinoma (n = 3), rectal carcinoma (n = 1), Hodgkin's lymphoma (n = 1) and sarcoma of the tongue (n = 1) or pelvis (n = 1). Five patients had systemic hypertension.

The definition of doxorubicin-induced systolic dysfunction was determined prospectively and based on the following three criteria: 1) ejection fraction <55% after doxorubicin, 2) decrease in ejection fraction of ≥10 ejection fraction units from the control value after doxorubicin, and 3) continued ejection fraction measurements of <55% after criteria 1 and 2 were met. Written informed consent was obtained from all patients. The study protocol was deemed ethical and approved by the Human Studies Committee at our institution.

Study protocol. Doxorubicin was administered intravenously as a bolus injection every 3 weeks in doses of 40 (n = 2), 50 (n = 8) and 60 (n = 16) mg/m^2. Patients also received noncardiotoxic doses of cyclophosphamide, vincristine, 5-fluorouracil, bleomycin or methylprednisolone. Each patient was evaluated within 24 h before the first treatment, 3 weeks after each treatment in which the cumulative doxorubicin dose was 40 to 60, 100 to 120, 150 to 180 and 200 to 240 mg/m^2, and 3 weeks after the peak doxorubicin dose. Fifteen patients selected at random were studied 1 h after the first doxorubicin treatment (early group). Twenty-two patients were studied 3 months after the last doxorubicin treatment (late group).

Patient evaluation included a history and physical examination to assess for heart failure using the New York Heart Association criteria, comprehensive two-dimensional, pulsed and Doppler color flow echocardiography and the average of three systemic blood pressure determinations (Critikon, Dinamap model 1846 SX/P). Echocardiographic studies were performed with the patient in the left semirecumbent position and analyzed without knowledge of clinical variables such as age, gender, height, weight and doxorubicin dose. Two-dimensional and pulsed Doppler echocardiograms were each analyzed without knowledge of the results of the other echocardiographic study. Studies selected for determination of intraobserver, interobserver and 3-week biologic variability of measured variables were examined ≥3 months apart.

Echocardiography and analysis. With use of a phased-array echocardiographic machine (Hewlett-Packard, model 77020) with a 2.5-MHz transducer, two-dimensional images were recorded on videotape in the left ventricular parasternal long-axis view, short-axis view at the mitral valve and papillary muscle levels and apical four-chamber, five-chamber, two-chamber and long-axis views. In an attempt to minimize foreshortening in the left ventricular long-axis view, an apical window was obtained that allowed rotation from the apical four-chamber to the two-chamber and long-axis views without apparent shifting of the apex from the center of the echocardiographic sector. Pulsed Doppler study of mitral inflow was performed by aligning the sample volume cursor on the immediate ventricular side of the mitral anulus from an apical four-chamber view as previously described (26,27). Proper placement of the sample volume was confirmed by assessing the position of the cursor with the simultaneous real time two-dimensional image. The sample volume cursor was placed in an intermediate position between the outflow tract and mitral valve to obtain left ventricular outflow and inflow velocities. All Doppler studies were recorded on hard copy at 100 mm/s. Color flow (velocity variance mode) and pulsed Doppler imaging were performed from appropriate views to exclude valvular regurgitation. To minimize variability in recorded studies, all echocardiograms in a given patient were performed by the same sonographer.

With use of a microcomputer interfaced with a Summagraphics plus digitizing tablet and customized software, the mitral Doppler velocity curve of five consecutive cardiac cycles was digitized as previously described (26,27). Individual indexes were obtained from each cardiac cycle and averaged. Diastolic filling indexes included peak early filling velocity, peak early to peak atrial filling velocity ratio, mean deceleration rate of early filling, deceleration time (measured as time interval from peak early filling velocity to the time where an imaginary line extrapolated from the descending limb of the early filling curve reaches zero) and acceleration time (measured as time from onset of mitral inflow to peak

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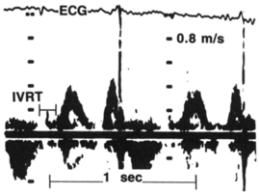

Figure 1. Pulsed Doppler echocardiographic tracing obtained in an intermediate position between the left ventricular outflow tract and mitral valve. The isovolumetric relaxation time (IVRT) was measured from the end of outflow to the beginning of inflow. ECG = electrocardiogram.

early filling velocity). Isovolumetric relaxation time was measured from the end of left ventricular outflow to the beginning of inflow (Fig. 1).

With use of a video computer system, the left ventricular endocardial surface was digitized on end-diastolic (that is, maximal area) and end-systolic (that is, minimal area) frames to obtain cross-sectional areas at the short-axis mitral valve (AM) and papillary muscle (AP) level. The leading edge technique as recommended by Wyatt et. al. (28) was used to trace endocardial edges. Ventricular length (L) at end-diastole and end-systole was measured by using an apical four-chamber view from the apex to the midpoint of an imaginary line at the mitral anulus. Ventricular volume (V) in end-diastole and end-systole was calculated by the modified Simpson's method, where $V = (L \times AM/3) + ([AM + AP] \times L/6) + (L \times AP/9)$ (29–33). Three ejection fraction determinations calculated in the usual fashion were averaged.

Statistical analysis. Values are expressed as mean value ± 1 SD. Analysis of variance for repeated measures (Scheffé F test) was used to assess differences in serial echocardiographic and blood pressure variables. An unpaired t test was used to assess differences between two groups. Chi-square analysis with correction for the size of the study groups was performed when appropriate. Correlations between Doppler variables and ejection fraction were sought with univariate least squares and multiple stepwise linear regression analyses (Statview-512+, BrainPower, Inc.). The percent variability (that is, intraobserver, interobserver and 3-week biologic variability) in a given variable was calculated as the absolute difference in the variable measured at two points in time divided by the mean value of the two measurements times 100%. A p value < 0.05 was considered statistically significant.

Results

Effect of doxorubicin on systolic function. Nine of the 26 patients developed doxorubicin-induced systolic dysfunction. In this group, ejection fraction began to decrease after a cumulative doxorubicin dose of 150 to 180 mg/m^2 from 66 ± 7% to 58 ± 7% ($p < 0.02$), with the maximal decrease occurring after the peak doxorubicin dose (45 ± 10%, $p < 0.001$) (Table 1). The decrease in ejection fraction was due to an increase in end-systolic volume. End-diastolic volume was unchanged. The isovolumetric relaxation time became prolonged as compared with control values after a cumulative doxorubicin dose of 100 to 120 mg/m^2 (66 ± 18 to 84 ± 24 ms, $p < 0.05$). The maximal prolongation in isovolumetric relaxation time occurred after the peak doxorubicin dose (115 ± 24 ms, $p < 0.001$). A significant prolongation in deceleration time and decrease in mean deceleration rate of

Table 1. Effect of Doxorubicin on Systolic Function and Diastolic Filling in the Nine Patients Who Developed Systolic Dysfunction

Index	Control	Cumulative Doxorubicin Dose (mg/m^2)				
		40 to 60	100 to 120	150 to 180	200 to 240	Peak
PE (cm/s)	56 ± 21	54 ± 17	57 ± 20	51 ± 18	50 ± 19	49 ± 15
PE/PA	1.03 ± 0.31	0.95 ± 0.29	0.92 ± 0.25	0.86 ± 0.25*	0.89 ± 0.29†	0.8 ± 0.21^
E-dec (cm/s^2)	460 ± 124	422 ± 166	426 ± 136	325 ± 118†	325 ± 118†	345 ± 122†
IVRT (ms)	66 ± 18	70 ± 25	84 ± 24†	101 ± 20‡	108 ± 24‡	115 ± 24§
DT (ms)	124 ± 18	139 ± 25	144 ± 28	170 ± 34*	169 ± 22†	173 ± 23*
AT (ms)	81 ± 17	77 ± 15	81 ± 17	84 ± 18	76 ± 7	78 ± 8
DFT (ms)	349 ± 96	340 ± 89	348 ± 106	345 ± 84	356 ± 97	348 ± 73
EF (%)	66 ± 7	62 ± 10	62 ± 9	58 ± 7*	51 ± 14‡	45 ± 10§
EDV (ml)	92 ± 15	91 ± 15	97 ± 20	91 ± 16	89 ± 22	92 ± 19
ESV (ml)	29 ± 9	29 ± 9	33 ± 11	35 ± 9	54 ± 19†	58 ± 18†
SBP (mm Hg)	109 ± 15	106 ± 15	110 ± 15	111 ± 16	107 ± 12	106 ± 12
DBP (mm Hg)	68 ± 8	62 ± 9	64 ± 9	66 ± 9	66 ± 9	66 ± 8
HR (beats/min)	83 ± 15	92 ± 10	87 ± 14	87 ± 11	82 ± 14	85 ± 10

*$p < 0.02$, †$p < 0.05$, ‡$p < 0.002$ and §$p < 0.001$ vs. control. AT = acceleration time of early filling; DBP and SBP = diastolic and systolic blood pressure, respectively; DFT = diastolic filling time; DT = deceleration time of early filling; E-dec = mean deceleration rate of early filling; EDV and ESV = end-diastolic and end-systolic volume, respectively; EF = ejection fraction; HR = heart rate; IVRT = isovolumetric relaxation time; PE = peak early filling velocity; PE/PA = peak early to peak atrial filling velocity ratio.

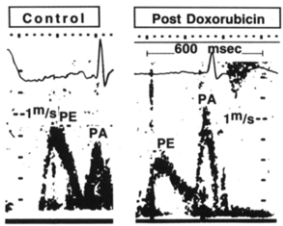

Figure 2. Case example demonstrating a striking decrease in peak early filling velocity (PE), peak early to peak atrial (PA) filling velocity ratio and mean deceleration rate of early filling of the transmitral filling velocity profile after treatment with doxorubicin (Post Doxorubicin) compared with filling before treatment (Control).

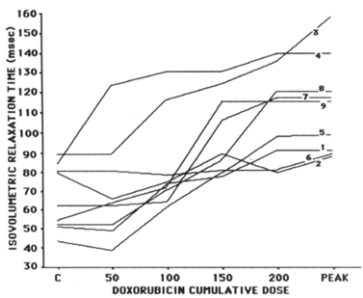

Figure 3. Individual changes in isovolumetric relaxation time from the control study (C) to cumulative doxorubicin doses of 40 to 60 (50), 100 to 120 (100), 150 to 180 (150) and 200 to 240 (200) mg/m^2 and after the peak dose in the nine patients who ultimately developed systolic dysfunction (patient numbers at right). Patient 1 developed doxorubicin cardiomyopathy and died of cardiogenic shock.

early filling and peak early to peak atrial filling velocity ratio occurred after a doxorubicin dose of 150 to 180 mg/m^2 (Fig. 2). In the 17 subjects not meeting criteria for doxorubicin-induced systolic dysfunction, ejection fraction, end-diastolic volume, end-systolic volume and all Doppler variables were unchanged with the exception of isovolumetric relaxation time, which slightly prolonged after a cumulative doxorubicin dose of 150 to 180 mg/m^2 (Table 2). Heart rate, diastolic filling time and blood pressure were unchanged after doxorubicin in both groups.

Prolonged isovolumetric relaxation time. In the nine patients who ultimately developed doxorubicin-induced systolic dysfunction, isovolumetric relaxation time was consistently prolonged before ejection fraction significantly decreased (Fig. 3 and 4). An increase in isovolumetric relaxation time >37% immediately before the cumulative doxorubicin dose that resulted in systolic dysfunction predicted development of doxorubicin cardiotoxicity in 78% (seven of nine patients) (Fig. 5). One of the nine patients (Patient 1) developed class IV congestive heart failure 3 weeks after the last doxorubicin dose and died of cardiogenic shock after a cumulative doxorubicin dosage of 200 mg/m^2. In this patient, ejection fraction was normal before the last doxorubicin dose, but isovolumetric relaxation time had increased by 57% (Fig. 1 and 2). In the 17 subjects who did not develop systolic dysfunction, 88% (15 of 17) had no prolongation in isovolumetric relaxation time >37% throughout the course of treatment (Fig. 5). Other Doppler variables such as peak early filling velocity, peak early to peak atrial filling velocity ratio, mean deceleration rate of early filling, deceleration time and acceleration time were not useful in predicting the development of doxorubicin-induced systolic dysfunction. The groups that did and did

Table 2. Effect of Doxorubicin on Systolic Function and Diastolic Filling in the 17 Patients Who Maintained Normal Systolic Function

Index	Control	Cumulative Doxorubicin Dose (mg/m^2)				
		40 to 60	100 to 120	150 to 180	200 to 240	Peak
PE (cm/s)	56 ± 15	53 ± 9	56 ± 12	57 ± 13	54 ± 12	54 ± 10
PE/PA	0.99 ± 0.28	1.00 ± 0.27	0.99 ± 0.3	0.94 ± 0.29	0.94 ± 0.3	0.97 ± 0.32
E-dec (cm/s^2)	402 ± 192	375 ± 161	438 ± 185	389 ± 140	380 ± 116	365 ± 130
IVRT (ms)	77 ± 20	79 ± 21	79 ± 18	91 ± 29*	90 ± 30*	90 ± 28*
DT (ms)	159 ± 54	166 ± 78	144 ± 46	163 ± 54	153 ± 33	161 ± 33
AT (ms)	81 ± 12	81 ± 20	82 ± 20	87 ± 18	86 ± 20	82 ± 18
DFT (ms)	385 ± 85	370 ± 68	382 ± 89	370 ± 62	369 ± 86	364 ± 84
EF (%)	65 ± 6	67 ± 6	67 ± 6	66 ± 5	65 ± 5	65 ± 5
EDV (ml)	92 ± 15	91 ± 15	97 ± 20	91 ± 16	90 ± 22	92 ± 19
ESV (ml)	32 ± 6	30 ± 7	33 ± 9	31 ± 8	30 ± 8	32 ± 9
SBP (mm Hg)	133 ± 23	131 ± 23	132 ± 23	131 ± 23	129 ± 23	129 ± 26
DBP (mm Hg)	76 ± 14	74 ± 13	73 ± 13	72 ± 12	70 ± 13	70 ± 13
HR (beats/min)	77 ± 10	77 ± 7	77 ± 8	79 ± 7	80 ± 10	80 ± 10

*$p < 0.05$ versus control. Abbreviations as in Table 1.

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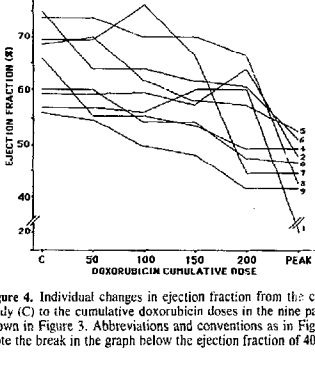

Figure 4. Individual changes in ejection fraction from the control study (C) to the cumulative doxorubicin doses in the nine patients shown in Figure 3. Abbreviations and conventions as in Figure 3. Note the break in the graph below the ejection fraction of 40%.

not develop systolic dysfunction demonstrated no differences in age (45 ± 12 vs. 49 ± 12 years, p = NS), gender (8 of 9 vs. 14 of 17 women, p = NS), total cumulative doxorubicin dose (273 ± 63 vs. 300 ± 66 mg/m^2, p = NS), presence of hypertension (1 of 9 vs. 4 of 17, p = NS) and control values for Doppler indexes and ejection fraction (Tables 1 and 2).

For the entire group after the peak doxorubicin dose, the percent change in isovolumetric relaxation time weakly correlated with the percent change in ejection fraction (Fig. 6). Multiple regression analysis demonstrated the percent change in isovolumetric relaxation time ($r = -0.44$, $p <$

Figure 5. Individual percent changes in isovolumetric relaxation time (IVRT) from the control study to the cumulative dose immediately preceding the dose that resulted in a significant decrease in ejection fraction in the 9 patients who ultimately developed systolic dysfunction (ABNL EF) and from the control study to the study after the peak dose in the 17 patients who did not develop systolic dysfunction (NL EF). A 37% change in isovolumetric relaxation time cutoff (**solid horizontal line**) had a 78% (7 of 9 patients) sensitivity and 88% (15 of 17 patients) specificity in predicting doxorubicin-induced systolic dysfunction ($p < 0.005$ by chi-square analysis corrected for the size of the study groups).

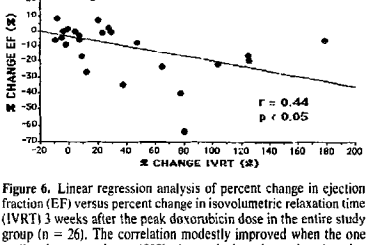

Figure 6. Linear regression analysis of percent change in ejection fraction (EF) versus percent change in isovolumetric relaxation time (IVRT) 3 weeks after the peak doxorubicin dose in the entire study group (n = 26). The correlation modestly improved when the one outlier demonstrating a 180% change in isovolumetric relaxation time and an unchanged ejection fraction was eliminated from the analysis ($r = -0.60$, $p < 0.005$).

0.05) to be the only predictor of percent change in ejection fraction. Other variables such as patient age, peak doxorubicin dose, presence or absence of hypertension and percent change in other Doppler indexes did not predict the percent change in ejection fraction. Lastly, the peak doxorubicin dose did not correlate with the percent change in isovolumetric relaxation time ($r = -0.26$, $p =$ NS).

Early and late effects of doxorubicin. In 15 patients (early group) selected at random, peak early filling velocity, peak early to peak atrial filling velocity ratio and ejection fraction increased and isovolumetric relaxation time shortened 1 h after the first dose of doxorubicin (Table 3). These changes returned to control values 3 weeks later. In 22 patients (late group) not receiving mediastinal chest irradiation after completion of chemotherapy, peak early to peak atrial filling velocity ratio, mean deceleration rate of early filling and ejection fraction decreased significantly and isovolumetric

Table 3. Early Effect of Doxorubicin on Systolic Function and Diastolic Filling in 15 Patients

Index	Control	First Doxorubicin Dose	
		1 h After	3 Weeks After
PE (cm/s)	59 ± 18	66 ± 19*†	56 ± 14
PE/PA	1.10 ± 0.24	1.22 ± 0.20‡§	1.09 ± 0.25
E-dec (cm/s^2)	497 ± 218	524 ± 190	458 ± 165
IVRT (ms)	74 ± 18	55 ± 14§‖	77 ± 23
DT (ms)	134 ± 25	135 ± 25	135 ± 36
AT (ms)	81 ± 13	88 ± 22	84 ± 16
DFT (ms)	380 ± 85	403 ± 103	356 ± 79
EF (%)	65 ± 6	74 ± 5‖¶	66 ± 7
EDV (ml)	92 ± 17	92 ± 18	88 ± 5
ESV (ml)	31 ± 7	24 ± 7†‡	30 ± 7
SBP (mm Hg)	121 ± 14	112 ± 17	114 ± 14
DBP (mm Hg)	70 ± 11	66 ± 11	67 ± 11
HR (beats/min)	77 ± 10	76 ± 10	80 ± 10

*$p < 0.05$, †$p < 0.005$, ‡$p < 0.001$ versus control. §$p < 0.05$, ‖$p < 0.01$, ¶$p < 0.002$ versus 3 weeks after the first dose. Abbreviations as in Table 1.

Table 4. Late Effect of Doxorubicin on Systolic Function and Diastolic Filling in 22 Patients

Index	Control	Peak Doxorubicin Dose	
		3 Weeks After	3 Months After
PE (cm/s)	58 ± 17	53 ± 12	50 ± 14*
PE/PA	1.01 ± 0.30	0.91 ± 0.30*	0.88 ± 0.30*
E-dec (cm/s²)	434 ± 208	370 ± 126*	344 ± 132*
IVRT (ms)	74 ± 20	98 ± 28†	96 ± 27†
DT (ms)	149 ± 52	157 ± 40	159 ± 34
AT (ms)	82 ± 13	84 ± 11	86 ± 10
DFT (ms)	376 ± 93	347 ± 85	369 ± 120
EF (%)	64 ± 6	59 ± 9*	59 ± 9*
EDV (ml)	89 ± 17	90 ± 19	89 ± 20
ESV (ml)	29 ± 7	36 ± 10*	36 ± 11*
SBP (mm Hg)	128 ± 22	120 ± 24	123 ± 23
DBP (mm Hg)	73 ± 12	67 ± 10*	68 ± 9
HR (beats/min)	79 ± 12	82 ± 11	81 ± 12

*$p < 0.05$ and †$p < 0.001$ versus control. Abbreviations as in Table 1.

relaxation time increased after the peak doxorubicin dose (Table 4). These changes were still evident 3 months after the last doxorubicin dose.

Variability of echocardiographic measurements. A single study selected at random for each patient (n = 26) was used to determine intraobserver variability of ejection fraction (5 ± 3%), end-diastolic volume (7 ± 6%), end-systolic volume (8 ± 6%), peak early filling velocity (2 ± 3%), peak early to peak atrial filling velocity ratio (5 ± 4%), mean deceleration rate of early filling (9 ± 10%), isovolumetric relaxation time (6 ± 8%), deceleration time (8 ± 10%) and acceleration time (8 ± 6%). A single study selected at random from 15 patients was used to determine interobserver variability of ejection fraction (5 ± 4%), end-diastolic volume (7 ± 5%), end-systolic volume (9 ± 7%), peak early filling velocity (3 ± 3%), peak early to peak atrial filling velocity ratio (7 ± 5%), mean deceleration rate of early filling (13 ± 12%), isovolumetric relaxation time (8 ± 10%), deceleration time (11 ± 12%) and acceleration time (11 ± 6%). To determine possible biologic variation in measured variables, 10 patients selected at random were studied before chemotherapy over a 3-week interval. The 3-week biologic variability was determined for ejection fraction (5 ± 4%), end-diastolic volume (8 ± 4%), end-systolic volume (9 ± 8%), peak early filling velocity (4 ± 3%), peak early to peak atrial filling velocity ratio (8 ± 6%), mean deceleration rate of early filling (17 ± 14%), isovolumetric relaxation time (9 ± 12%), deceleration time (13 ± 13%) and acceleration time (12 ± 7%). The absolute intraobserver, interobserver and 3-week biologic differences in ejection fraction were, respectively, 3 ± 2 ejection fraction units (range 0 to 5), 3 ± 2 ejection fraction units (range 0 to 9) and 3 ± 3 ejection fraction units (range 0 to 6).

Discussion

Detection of doxorubicin toxicity. Doxorubicin is a widely used and efficacious antineoplastic agent (1–3). However, significant irreversible and unpredictable cardiotoxicity makes its use problematic (4–7). At present, noninvasive testing is commonly used to guide doxorubicin chemotherapy; although endomyocardial biopsy delineates actual myocardial damage, it is invasive and not routinely used. Most noninvasive tests have measured indexes of systolic function as a means of detecting doxorubicin cardiotoxicity. Studies using systolic time intervals have shown variable results (8). M-mode echocardiography has not contributed greatly to the monitoring of cardiac function in this setting. The fractional shortening of the minor diameter of the left ventricle and velocity of circumferential fiber shortening have been used, but are critically dependent on synchronous ventricular wall motion and loading conditions. It is unknown whether M-mode echocardiographically derived indexes of diastolic filling are useful predictors of doxorubicin cardiotoxicity (34). Ejection fraction has been found useful in the determination of doxorubicin cardiotoxicity (13). However, it is not an ideal index and reports (35) have shown that it correlates poorly with myocardial biopsy grades of doxorubicin cardiotoxicity and some investigators (13–15) have questioned the sensitivity of the rest ejection fraction. The need for a sensitive and specific noninvasive test of doxorubicin cardiotoxicity prompted the present study.

Doxorubicin cardiotoxicity. In our study, doxorubicin administration was found to prolong isovolumetric relaxation time and deceleration time and to decrease peak early to atrial filling velocity ratio and deceleration rate of early filling. A 37% prolongation of the isovolumetric relaxation time was 78% sensitive and 88% specific in detecting doxorubicin-induced systolic dysfunction. Other Doppler indexes and clinical variables were not predictive of doxorubicin-induced change in ejection fraction. Doxorubicin enhances diastolic filling and ejection fraction by 1 h of administration. The impairment in diastolic filling and systolic function induced by doxorubicin persists ≥3 months after treatment.

Effect on diastolic function. In a retrospective study, Lee et al. (17) showed alterations in left ventricular diastolic filling with radionuclide techniques after the completion of doxorubicin treatment in 12 patients with a left ventricular ejection fraction >55%. This study suggested that filling indexes of diastolic function may be more sensitive than variables of systolic function. More recently, Marchandise et al. (18) showed a significant prolongation in pulsed Doppler-derived isovolumetric relaxation time and time to peak filling and a decrease in peak early filling velocity, peak early to atrial filling velocity ratio and deceleration rate in 19 patients receiving a mean cumulative doxorubicin dose of 240 ± 135 mg/m². In the present study, similar alterations of diastolic filling and isovolumetric relaxation time were demonstrated in patients who ultimately developed doxorubicin-induced systolic dysfunction. Although most of the Doppler

indexes were altered by doxorubicin therapy, the isovolumetric relaxation time was the only Doppler index that was significantly prolonged before ejection fraction decreased significantly and that predicted doxorubicin-induced systolic dysfunction.

The mechanism that accounts for the alteration in isovolumetric relaxation time and filling is unknown. Although, Doppler-derived indexes are not precise measures of intrinsic diastolic function, it is likely that impairment in left ventricular relaxation accounts for the prolonged isovolumetric relaxation time and impaired filling seen with doxorubicin administration (26,27). No obvious changes in preload and afterload were evident as assessed by end-diastolic volume and systolic blood pressure, respectively. Damage to myocardial membranous structures and mitochondria have been demonstrated after usual clinical doses of doxorubicin and could account for long-term changes in left ventricular relaxation and filling (36).

Early- and late-term effects of doxorubicin. The early and late effects of doxorubicin on isovolumetric relaxation time, diastolic filling and ejection fraction strikingly differed. As in the study of Brown et al. (19), doxorubicin enhanced left ventricular systolic function, diastolic filling and isovolumetric relaxation time by 1 h after administration. The mechanism accounting for such changes may relate to a positive inotropic and lusitropic effect of doxorubicin. Doxorubicin may act to increase intracellular calcium concentration by inhibiting adenosine triphosphate-dependent sodium-potassium channels or enhancing the release of catecholamines (37–39). The late (3 months) depression in systolic function, diastolic filling and isovolumetric relaxation is more likely due to myocardial injury (8,10–12). The degree of systolic and diastolic dysfunction did not correlate with the cumulative doxorubicin dose. This finding is consistent with data from prior studies (5) demonstrating that myocardial dysfunction due to cellular injury from doxorubicin is complex and nonlinear.

Limitations of study. Measures of left ventricular ejection fraction and volumes are usually deemed most reliable when derived from contrast or radionuclide ventriculography. However, the reliable calculation of left ventricular ejection fraction and volumes by two-dimensional echocardiography using methods identical to those in the present study has been demonstrated (28–33). In addition, the accuracy of ejection fraction derived by echocardiography is enhanced in subjects lacking segmental wall motion abnormalities, as was the case in the present study. Patients served as their own control and serial changes in ejection fraction should reflect true alterations of systolic function. The relatively small interobserver, intraobserver and biologic variability of the two-dimensional echocardiographic measurements supports this view. Although the results of the present study are probably applicable to prior studies utilizing radionuclide-derived ejection fraction, this has yet to be shown. In the absence of the development of congestive heart failure, no standard definition of doxorubicin cardiotoxicity exists. However, the definition used in the present study was prospective, reasonably strict and in parallel with clinical guidelines in the use of doxorubicin.

Conclusions. Prolonged isovolumetric relaxation time and impaired diastolic filling were demonstrated with Doppler echocardiography in patients who ultimately developed doxorubicin-induced systolic dysfunction. Prolongation of the isovolumetric relaxation time was found to be a useful predictor of the development of reduced ejection fraction due to doxorubicin. The isovolumetric relaxation time may help guide the need for endomyocardial biopsy in patients who require higher doses of doxorubicin but experience no depression in ejection fraction. Doxorubicin enhances isovolumetric relaxation, diastolic filling and ejection fraction by 1 h after administration. Abnormalities in isovolumetric relaxation and diastolic filling persist ≥3 months after doxorubicin administration.

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