Acta Oncologica Vol. 33, No. 6, pp. 645–649, 1994

CARDIAC DIASTOLIC FUNCTION IN PEDIATRIC PATIENTS RECEIVING DOXORUBICIN

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The purpose of the study was to compare systolic and diastolic function in pediatric patients treated with doxorubicin. Left ventricular function was evaluated in 61 children prior to and following chemotherapy. None had clinical evidence of cardiac decompensation prior to treatment. All received relatively low cumulative doses of doxorubicin; the majority received the drug by continuous infusion. Systolic function was estimated using fractional shortening; diastolic function was estimated using A wave velocity, E wave velocity, E to A ratio, and deceleration time. There was a small but significant decline in systolic cardiac function as estimated from changes in fractional shortening that could not be appreciated in any of the measured parameters of diastolic function. A variety of reasons that could be responsible for the absence of significant changes in diastolic function are discussed. For the present, estimations of systolic function are preferred over the studied parameters of diastolic function in the evaluation of cardiac status in pediatric patients receiving doxorubicin containing regimens.

Doxorubicin is an anthracycline antibiotic with a broad spectrum of clinical activity as an antineoplastic agent (1). It is effective in the treatment of hematologic malignancies and solid tumors and is widely used in both the pediatric and adult populations. Unfortunately, doxorubicin demonstrates a cumulative dose-related cardiotoxicity that often requires the discontinuation of the drug at a point during therapy when the tumor is still responsive (2). Patients receiving this drug differ considerably in the cumulative dose tolerated; some develop cardiac dysfunction at relatively low cumulative dosages, while others tolerate cumulative dosages considerably greater than the usual maximum recommended dose. It is well recognized that patients are best served if doxorubicin can be continued until additional administration either will not result in further oncologic improvement or will contribute to clinically significant cardiac toxicity (3).

Several methods have been utilized to estimate doxorubicin-related cardiac toxicity. The most commonly used are measures of systolic function determined by either echocardiographic or nuclear imaging (4–8). In the pediatric population the echocardiogram has several advantages: data are accumulated in real time, thus reducing problems associated with movement, and portable equipment for bedside studies is available. Additionally, echocardiography is less costly and does not use radioactive isotopes. Unfortunately, while echocardiography assists in identifying injury to the myocardium that has already taken place, it is not an ideal predictor of damage that is likely to occur if additional doxorubicin is administered (9). Cardiac biopsy with electron microscopic evaluation of cardiac ultrastructure often demonstrates cardiac changes at lower cumulative doses than can be detected by currently available non-invasive estimations of myocardial function (10). Cardiac biopsies, however, are costly, pa-

Received 28 September 1993.
Accepted 26 March 1994.
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Portions of this paper were presented at 18th International Congress of Chemotherapy, Stockholm, Sweden, June 27–July 2, 1993.

 ISSN 0284-186X

tients are exposed to radiation, and the techniques are invasive with a small risk of morbidity associated with the procedure. While cardiac biopsies are widely used in some centers for adult patients, they have been utilized less in children. An ideal test for following patients receiving doxorubicin might combine the predictive value of the biopsy with the safety, convenience, and noninvasive nature of the echocardiographic study.

Diastolic cardiac function is an important concept that has recently received considerable attention (11). Normal diastolic function depicts complex physiologic processes involving multiple factors, both passive and metabolically active, which enable the myocardium to relax, and expand the ventricular cavities, thereby allowing blood to enter from the atria without sustaining inordinate increases in filling pressures. Several Doppler measurements for estimating diastolic function have been identified; these include acceleration time, the time velocity integral, early diastolic deceleration time, isovolumic relaxation time, peak filling rate, and peak early- and late-filling velocities (12).

Some authors have suggested that abnormalities of diastolic function may exist in a considerable number of patients who have preserved systolic function (13, 14). To investigate the clinical usefulness of changes in diastolic function following doxorubicin therapy we undertook the following study.

Material and Methods

Sixty-one patients, ranging in age from 7 months to 15.5 years, were included in this retrospective analysis. There were 29 boys and 32 girls, who represented a subgroup of a much larger population that had been followed at The University of Texas M. D. Anderson Cancer Center for cardiac changes associated with doxorbuicin chemotherapy. The unifying factors for this subgroup were their young age, their normal cardiac function at the time of the initial doxorubicin treatment, and the fact that they had not received mediastinal irradiation. These children had a variety of hematologic and solid malignancies as summarized in Table 1.

All patients were treated with doxorubicin; 50 received the drug over 24 h as a continuous infusion, 10 were treated with a 1-h infusion, and one received a 6-h continuous infusion and was included with those who received the drug by rapid infusion. The mean cumulative dose of doxorubicin for the entire group was 284 mg/m^2 (119.13 SD, range 50–475 mg/m^2). When the cumulative dose for those patients who received the drug by continuous infusion was corrected for differences in toxicity between standard and continuous infusion schedules (3), the corrected cardiotoxic equivalent dose for our patients was 204.87 mg/m^2 $\pm$ (76.873 SD, range 35–329 mg/m^2). Doxorubicin was given in combination with a variety of other agents summarized in Table 2.

All of these patients had undergone a pre- and posttreatment cardiac evaluation that included a cardiac history, physical examination, standard 12-lead electrocardiogram, and an ultrasound investigation. In addition, several patients had more than one posttreatment evaluation during their long-term followup.

Ultrasound investigations consisted of M-mode, two-dimensional, and Doppler echocardiographic studies using H-P Sonos 1000 (Hewlett-Packard, Andover, Massachusetts, USA) imaging equipment. M-mode echocardiographic images were recorded at a paper speed of 100 mm/s at the level of papillary muscle of the left ventricle, the mitral valve, and the aortic root. Similarly, recordings of the pulmonic and tricuspid valves were made. Measurements of end-systolic and end-diastolic left ventricular dimensions were used to estimate fractional shortening (FS), as a parameter of systolic function. Reference electrocardiograms were simultaneously recorded.

Table 1

Malignancies in 61 pediatric patients treated with doxorubicin

Malignancy	Number of patients	
	Full group of 61 patients	Subgroup of 41 patients
Osteosarcoma	18	13
Ewing's sarcoma	12	11
Hodgkin's disease and non-Hodgkin's lymphoma	8	7
Neuroblastoma	6	2
Rhabdomyosarcoma	5	1
Nasopharyngeal carcinoma	4	3
Wilms' tumor	2	2
Hematologic malignancies	2	1
Miscellaneous malignancies*	4	1

* One each: uncharacterized sarcoma, ovarian carcinoma, desmoid fibromatosis, and synovial sarcoma.

Table 2

Antineoplastic agents administered in combination with doxorubicin in 61 pediatric patients

Agent	Number of patients
Cyclophosphamide	37
Vincristine	36
Cisplatin	27
Etoposide	25
Ifosfamide	23
Mesna	22
Actinomycin D	14
Methotrexate	5
Bleomycin	5
Dacarbazine	5
Nitrogen mustard	5
Vinblastine	6
Procarbazine	4
Arabinoside C	4
6-Mercaptopurine	3
Carboplatin	2
Thiotepa	2
Chlorambucil	1
Asparagine	1

Real time 2-dimensional echocardiograms were recorded on videotape in standard parasternal long- and short-axis views, in apical views in two-, four- and five-chamber planes, and in subcostal views in the four-chamber plane. Flow velocity studies using pulsed- and continuous-wave Doppler signals were recorded across all four cardiac valves. The flow velocity across the mitral valve was recorded in both pulsed- and continuous-wave Doppler modes from the apical two- and four-chamber views. The sample volume for pulsed-Doppler waves was placed in the inflow of the left ventricle, midway between the annulus and the tip of the mitral valve leaflets. Flow velocity across the tricuspid valve was recorded from the apical four-chamber view using both pulsed- and continuous-wave Doppler signals. Imaging was initially attempted using a 3.5 MHz transducer. Supplemental imaging was then undertaken if necessary, using either 2.5 or 5.0 MHz transducers. All images were considered to be of technically good or excellent quality. A computer-based digitizing program developed by the Digisonics Corporation (Houston, Texas, USA) was used to estimate the final values in this analysis. Four parameters of left ventricular diastolic function were studied: mitral valve peak E wave velocity (onset of early-diastole or rapid-filling phase), peak A wave velocity (onset of late-diastole and atrial contraction), E to A ratio, and deceleration time (time from peak E velocity until the velocity of blood flow returns to baseline). In order to minimize errors, and obviate the effects of respiratory variation on cardiac function, the mean of several cycles was used to determine the reported values.

In all, 391 echocardiographic studies were performed on the 61 patients. The pretreatment, the earliest posttreatment, and the lowest late values of systolic and diastolic function formed the basis for the present analysis. The earliest posttreatment FS determination was obtained within one week of the conclusion of doxorubicin therapy in 50 of the 60 patients; all but 4 were studied within two months of completing treatment. Late studies were obtained during subsequent follow-up visits; the longest follow-up was obtained 4.5 years after therapy.

The mean values and standard deviations for systolic and diastolic function parameters were used to evaluate the significance of change following doxorubicin. In all of the 61 patients, parameters of systolic function were available; a subgroup of 41 had pre- and posttreatment technically good or excellent quality Doppler studies which allowed for measurement of diastolic parameters. The systolic function of the smaller subgroup of 41 patients was analyzed separately to create a uniform population for the comparison of systolic and diastolic function. The data for both groups are shown in Table 3 and significance was determined using paired t-tests.

Table 3

Mean values and significance of FS and various parameters of diastolic function in 61 pediatric patients treated with doxorubicin

	NL value*	Pretreatment	Posttreatment	p-value†
Systolic function				
FS (n = 61)	36 (6.2 SD)	34.78	33.36	0.015
FS (n = 41)	36 (6.2 SD)	34.54	33.15	0.054
Diastolic function (n = 41)				
Peak A wave velocity (cm/s)	49 (8 SD)	54.08	50.90	0.23
E/A ratio	1.87 (0.39 SD)	1.74	1.84	0.26
Peak E wave velocity (cm/s)	91 (11 SD)	89.92	89.20	0.83
Deceleration time (milliseconds)	193 (23 SD)	196.22	196.34	0.99

* Normal values compiled from Snider AR et al. (14); Meliones JN et al. (22); and Gidding SS (23).
† Significance was determined using paired t-tests.

Results

None of the 61 patients had clinical or echocardiographic evidence of cardiac dysfunction prior to receiving doxorubicin. Neither clinical signs nor symptoms of congestive failure developed in any of the patients during the period of study. None of the pretreatment FS values were below the institutional lower limit of normal ($\leqslant 27$). Four patients had mildly increased FS values (41–43) and one patient had a moderately elevated pretreatment FS of 48. The mean FS value for the group was 34.780 (3.81 SD; range 29–48). The median for the group was 34, suggesting that the values were symmetrically distributed around the mean. For the entire group, the mean of the earliest posttreatment fiber shortening value was 33.356 (3.04 SD; 27–40), and the difference between the pretreatment and earliest posttreatment mean value for the group was significant ($p = 0.015$). When corrected for cardiotoxic equivalent dose (3), there was no difference in FS changes between the 50 patients who received the drug over 24 h when compared with the 11 who received the drug by 1- or 6-h infusions. Five of the patients ultimately developed FS values which fell below the institutional normal range; one was noted at the conclusion of chemotherapy, and four during the follow-up observation period.

For the 41 patients in whom diastolic function could be evaluated, the mean FS values before the after treatment were almost identical to those obtained for the larger group (34.537 versus 34.780 for the pretreatment values, and 33.146 versus 33.356 for the posttreatment values respectively). The higher p value ($p = 0.054$) is a reflection of the smaller number of patients available for analysis (Table 1). From the standpoint of their cardiac response to doxorubicin, there were no characteristics suggesting that the subgroup of 41 was different in any way from the 61 patients. Among the four parameters of diastolic function studied, the peak A wave velocity correlated best with the systolic function, and decreased slightly, from 54.078 cm/s (13.774 SD; range 25.31–84.82) before treatment to 50.898 cm/s (11.772 SD; range 30.54–86.40) following treatment. This decrease demonstrated a weak trend toward significance ($p = 0.23$). The values for the peak E wave velocity, the E to A ratio and the deceleration time demonstrated no significance (Table 1).

Discussion

Individualizing doxorubicin dosage is a dilemma. Ideally, as long as the drug remains effective, it should be continued until the next dose, had it been given, would have resulted in clinically significant cardiac dysfunction. Even with sophisticated non-invasive studies and cardiac biopsies, the question of when to stop treatment remains problematic (3). Resting ejection fractions and FS values identify existing cardiac damage, but as the dose-versus-congestive heart failure curve of doxorubicin is hyperbolic (15), detecting changes in cardiac function before overt heart failure occurs is not always possible.

Methods of reducing the likelihood of cardiac damage are also suboptimal; extending the infusion time of doxorubicin allows considerably larger cumulative doses to be administered, but cardiotoxicity may still occur (16). Cardiac protectors are under study, but they, too, do not fully eliminate the risk of cardiac toxicity (17). Several guidelines and algorithms have been published suggesting ways in which cardiotoxicity may be minimized; none is ideal (3, 18).

Diastolic cardiac dysfunction may exist in patients with preserved systolic function. This is especially true when the underlying abnormality results in left ventricular hypertrophy, increased myocardial fibroses, myocardial ischemia, or left ventricular pressure overload (19, 20). Patients in whom diastolic dysfunction precedes changes in systolic function may demonstrate normal ejection fractions at rest, but have reduced exercise capacity, increased chamber filling pressures at normal filling volumes, and increased pulmonary capillary occlusion pressures during exercise (14, 21–23). If early changes in diastolic function could be consistently identified in patients being treated with doxorubicin before significant cardiac damage occurs, more accurate determination of the maximum tolerated dose of an individual patient could be achieved.

In the pediatric population of our study, the mean cumulative cardiac equivalent dose of doxorubicin was relatively low. Although none of our patients developed clinically significant congestive heart failure, 5 nevertheless, experienced reductions in FS into the abnormal range. The fact that there was a small but significant drop in FS between the pretreatment and posttreatment determination shows that some change in cardiac function had already taken place. It is at this dose level that detection of cardiac changes would be extremely useful, i.e., when subclinical damage may have already occurred without clinical evidence of myocardial dysfunction. The markers of diastolic function that we considered did not appreciate these subtle changes in the study population at this dose level, even though the systolic parameter did. For each patient in the study, systolic and diastolic parameters were measured simultaneously. Our conclusion that changes in systolic function were more readily detected than were changes in diastolic function should be valid, depsite the facts that some patients received higher cumulative dosages and that some were studied after longer intervals from the time of their last treatment. While some of our patients received additional agents, which may augment cardiac toxicity when given together or sequential to doxorubicin, it is unlikely that such an interaction would selectively affect either systolic or diastolic function.

The most likely explanation of our failure to appreciate changes in diastolic function is that parameters of systolic

function represent a better tool for detecting early cardiac changes associated with doxorubicin in the pediatric population. There are, however, a number of other considerations that also must be taken into account: young patients may demonstrate changes in diastolic function relatively later in the course of their disease than adults (21). Much less likely is the fact that most of our patients received doxorubicin by continuous infusion, and in such patients systolic and diastolic function may behave differently than had the drug been given according to a standard treatment schedule. Finally, present estimations of diastolic function represent a relatively new clinical tool which is more difficult to measure and interpret than are the well-established parameters of systolic function.

For the present, predictions of cardiac damage based on determinations of diastolic function in pediatric patients treated with relatively low cumulative dosages of doxorubicin given by continuous infusion, remains problematic. Such determinations cannot be recommended as the sole predictor of future cardiotoxicity when additional doxorubicin is to be administered. Even changes in systolic function, especially at fairly low cumulative dosages, provide inadequate data to make a decision to continue or to stop doxorubicin for most patients. That decision is complex and, with the presently available methods, should not be made solely on the basis of a single laboratory determination. Patients are best served if the decision includes data regarding the equivalent cumulative doxorubicin dose and clinical assesment, as well as the results of cardiac studies.

As better methods of cardiac imaging evolve, as additional markers of diastolic function are recognized and as experience in using these techniques is acquired, the use of diastolic function measurements for patients undergoing treatment with doxorubicin may gain importance. Additional studies are necessary to ascertain if our conclusions apply to older patients, to patients who have been concomitantly treated with cardiac protectors, or to those who have been evaluated with other parameters of diastolic function.

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