DIAGNOSTIC NUCLEAR MEDICINE

The Importance of Adequate Exercise in the Detection of Coronary Heart Disease by Radionuclide Ventriculography

Thomas J. Brady, James H. Thrall, Ka Lo, and Bertram Pitt

The University of Michigan Medical Center, Ann Arbor, Michigan

Rest and exercise radionuclide ventriculograms were obtained on 77 symptomatic patients without prior documented coronary artery disease (CAD). Coronary artery disease was present by angiograms in 48. Radionuclide ventriculography (RNV) was abnormal in 41 patients (overall sensitivity 85%). In 29 patients with normal coronary arteries, RNV was normal in 24 (specificity 83%). To determine if the exercise level affects sensitivity, the studies were graded for adequacy of exercise. It was considered adequate if patients developed (a) chest pain, or (b) ST segment depression of at least 1 mm, or (c) if they achieved a pressure rate product greater than 250. Among the 48 patients with coronary artery disease, 35 achieved adequate exercise. Thirty-three had an abnormal RNV (sensitivity 94%). In 13 patients who failed to achieve adequate exercise, RNV was abnormal in eight (sensitivity of only 62%). Some patients with coronary artery disease may have a normal ventricular response at inadequate levels of stress.

J Nucl Med 21: 1125–1130, 1980

Patients with hemodynamically significant coronary artery disease may have normal ventricular function at rest, and develop ventricular dysfunction only during stress when imbalances between circulatory supply and demand become evident. In these patients, stress-induced myocardial ischemia can be detected objectively with electrocardiographic changes and recognized subjectively by anginal symptoms (*1,2*). Using supine bicycle exercise, Borer et al. (*3,4*) demonstrated that gated equilibrium blood-pool imaging is a sensitive technique for identifying patients with exercise-induced ventricular dysfunction. However, with this type of exercise some patients are limited by leg fatigue before symptomatic or electrocardiographic changes are reached. Thus, some patients with significant coronary artery disease may have a normal ventricular response with inadequate stress only to develop ventricular dysfunction if higher levels of exercise could be achieved (*5*). The present study was undertaken to determine the sensitivity of stress radionuclide ventriculography in detecting patients with coronary artery disease, as related to the adequacy of exercise achieved.

Received March 24, 1980; revision accepted Aug. 8, 1980.

For reprints contact: James H. Thrall, MD, Div. of Nuclear Medicine, Univ. of Michigan Medical Ctr., Ann Arbor, MI 48109.

MATERIALS AND METHODS

Seventy-seven patients comprising the population of this study were selected from a larger group of 133 patients undergoing both exercise RNV and coronary angiography for evaluation of chest-pain syndromes. We excluded 56 patients with documented CAD—i.e., diagnostic Q waves, prior documented myocardial infarction, or coronary artery bypass graft surgery. There were 59 males and 18 females with a mean age of 49. Thirteen patients were receiving propranolol at the time of the study. No patient had clinical evidence of congestive heart failure. Patients with valvular heart disease and myocarditis were also excluded before selection of the original 133 patients. Informed consent was obtained before both procedures.

Rest and exercise multigated blood-pool scintigraphy was performed as previously described (*5*). Briefly, patients were given 25 mCi of Tc-99m for in vivo red-blood-cell labeling (*6*). Data were acquired on a standard gamma camera equipped with a low-energy, parallel-hole, high-sensitivity collimator and interfaced to a minicomputer. R-wave-synchronized data were collected in a 64 × 64 matrix format using a computer program providing up to 14 frames per cardiac cycle. During the resting studies the maximum time per frame was 50 msec to provide adequate temporal resolution (*7*). During the exercise studies, the time per frame was computer-controlled depending on the exercise heart rate.

All studies were obtained in the supine position. Resting studies used a 10° right anterior oblique (RAO) view and the left anterior oblique (LAO) view that best separated the right and left ventricles. Baseline heart rate, blood pressure, and electrocardiogram were obtained. Patients were monitored during the study with a bipolar CM-5 lead system. Patients were exercised with a bicycle ergometer, maintaining a pedaling rate of 50 to 60 RPM. After a warmup period of 1 min at 150 KPM the workload was gradually increased until the patient reached a preset heart rate between 90 and 100. The heart rate was kept constant during data acquisition with minor adjustments in the workload. During the acquisition, the heart rate, blood pressure, and ECG were monitored. Upon completion of the acquisition, the workload was increased by 150 KPM. When the heart rate stabilized the acquisition was repeated. Patients were exercised in this manner until symptom limiting chest pain, leg fatigue, or shortness of breath developed. The exercise was not stopped when patients developed only mild to moderate chest pain or when ST segment depression occurred. By analyzing the heart rate, blood pressure, ECG, and chest-pain response during exercise, a set of criteria was established to grade the adequacy of exercise.

The ejection fractions (EF) were calculated from the rest and exercise LAO radionuclide studies using a commercial edge-detection program with varying regions of interest (*8*). The ejection fractions obtained in this manner have been shown in our laboratory to correlate well among observers and with ejection fractions obtained with contrast ventriculography at rest and during exercise (*9*). Based on these findings, an exercise-induced rise in ejection fraction of greater than 0.05 in any patient was considered significant. Ventricular wall motion was analyzed by viewing cinematic closed-loop displays of rest and exercise LAO radionuclide ventriculograms. A normal radionuclide study includes: (a) a resting EF >0.50, (b) an exercise EF >0.05 above the resting value, and (c) normal wall motion at rest and during exercise.

Multiple-view coronary angiograms were obtained on all patients using the Sones technique. Seventy-one percent of studies were obtained within 1 wk, and all were made within 4 mo of the radionuclide study. All patients had single-plane resting contrast ventriculograms. In addition, 56 patients (73%) had exercise contrast ventriculograms as previously described (*10*). Significant CAD was defined as a greater than 70% reduction in the diameter of at least one coronary artery. Normal coronary arteries were defined as any with <50% stenosis. There were no patients with a single lesion between 50 and 70%. Contrast ventriculograms were evaluated for regional wall-motion abnormalities by viewing cineangiographic displays of rest and exercise studies. All contrast studies were interpreted by two cardiologists on a routine clinical basis. The radionuclide studies were evaluated by two nuclear medicine physicians with knowledge of a patient's history but without knowing the results of the contrast studies.

Rest and exercise radionuclide data were compared using the paired and unpaired t-test. The chi square and Fisher exact test were used to analyze group data.

RESULTS

Forty-eight of the 77 patients had significant coronary artery disease. The radionuclide study was abnormal in 41 of these patients (sensitivity 85%, Table 1). Thirty-seven patients had an abnormal ejection fraction response (77%), while 30 patients had a regional wall-motion abnormality (62%). The mean resting ejection fraction in 48 patients with coronary artery disease was 63.4% ± 1.4 (standard error of the mean) and during exercise was 61.1% ± 1.7 (Fig. 1). The sensitivity of the radionuclide study was not significantly different in single-, double-, or triple-vessel disease.

The mean ejection fraction in 29 patients with normal coronary arteriograms was 61.6% ± 2.2 at rest and 69.6% ± 2.6 during exercise (Fig. 1). In this group, the radionuclide study was normal in 24 and abnormal in five patients (specificity 83%, Table 1). Table 2 summarizes the data from the five false-positive studies. Three of the five patients (A, B, and C) had an abnormality of rest and/or exercise regional wall motion present on contrast ventriculography. The radionuclide wall-motion analysis agreed completely in these three

TABLE 1. SENSITIVITY AND SPECIFICITY OF EXERCISE RNV IN DETECTING CAD COMPARED TO CORONARY ANGIOGRAPHY (C.A.)

	C.A.	
	Positive	Negative
RNV		
Positive	41	5
Negative	7	24
Sensitivity = 85%		
Specificity = 83%		

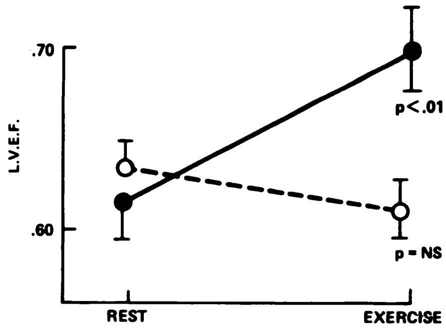

FIG. 1. Mean rest and exercise left-ventricular ejection fraction (LVEF), with standard error of the mean, in 29 patients with normal coronaries (O - - - O) and in 48 patients with CAD (O - - - O).

patients and signified the presence of ventricular dysfunction in the presence of normal coronary arteries.

The exercise data from the 77 patients were evaluated for adequacy of exercise. A study was graded adequate if patients achieved any one of the following three criteria during exercise: (a) chest pain, (b) flat ST segment depression greater than 1 mm, or (c) a PRP greater than 250. (PRP = (pressure-rate product) systolic blood pressure × heart rate ÷ 100.) The PRP value of 250 is used in our treadmill laboratory and is supported by previous work (*11*). Chest pain was elicited by the physician performing the study and was recorded as simply present or absent. In 48 patients with coronary artery disease, 35 achieved adequate exercise, and 33 had an abnormal RNV (sensitivity 94%, Table 3). Thirteen patients with significant CAD did not achieve adequate exercise; of these, eight had an abnormal RNV (sensitivity only 62%). The distribution with respect to chest pain, ST segment change, and PRP is given in Fig. 2. Chest pain was experienced in 44% of patients with coronary artery disease and in 24% of those without CAD. ST segment depression was present in 31% of CAD patients and in only one without. The non-CADs were more likely to reach an adequate pressure-rate product (38%) than those with coronary artery disease (19%).

Twenty-one patients with CAD experienced chest pain during supine exercise. Sixteen of 21 had an abnormal ejection-fraction response. The mean ejection fraction in this group was 65.2% at rest and 60.3% during exercise (Table 4). Of the six patients with normal global function, five had regional wall-motion abnormalities (sensitivity 95%). The sensitivity of regional wall-motion abnormalities alone was 71%.

TABLE 3. SENSITIVITY OF RNV RELATED TO LEVEL OF EXERCISE

	True positive	False negative	Sensitivity (%)	
Adequate exercise	33	2	94	
Inadequate exercise	8	5	62	p <0.02

Sixteen patients developed greater than 1 mm ST-segment depression during exercise. One of these was a patient with normal coronary arteries who had a normal ventricular response to exercise. The other 15 patients had coronary artery disease and all had a regional wall-motion abnormality during exercise (Table 4). The mean ejection fraction was 62.8% at rest and 55.7% during exercise in this group. Two patients had normal left-ventricular ejection fraction response, but these patients developed regional wall-motion abnormalities with exercise. There was no relationship to the degree of ST-segment depression and the fall of ejection fraction.

Only nine patients with coronary artery disease achieved a PRP greater than 250 (Table 4). Eight of nine patients had abnormal global ejection-fraction response (sensitivity 89%). The mean ejection fraction was 63.7% at rest and 60.5% during exercise. Six of nine had a regional wall-motion abnormality. One patient had a completely normal study.

In patients with CAD who achieved any two criteria for adequate exercise, the mean ejection fraction was 63.7% at rest and 54.0% during exercise. One patient had a normal left-ventricular ejection fraction response. All

TABLE 2. FALSE-POSITIVE RADIONUCLIDE STUDIES

Pts.	Radionuclide EF Rest Exercise	Radionuclide Wall Motion Rest—Exercise	Contrast wall motion Rest—Exercise
A	0.42† − 0.37*	nl—abn	nl—abn
B	0.48† − 0.48*	abn—abn	abn—xxx
C	0.47† − 0.34*	abn—↑abn	abn—↑abn
D	0.79 − 0.73*	nl—nl	nl—nl
E	0.43† − 0.50	nl—nl	nl—nl

* Abnormal EF response to exercise.
† Abnormal rest EF.

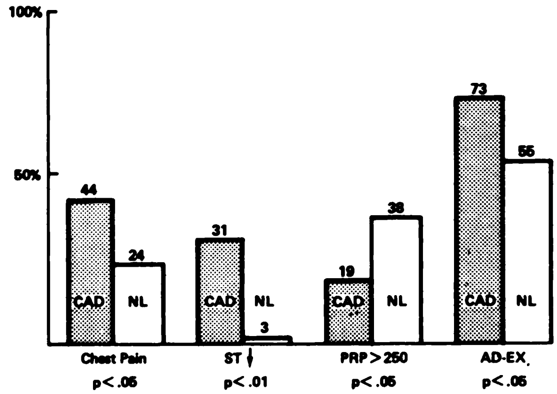

FIG. 2. Percentages of patients with CAD (stippled, N = 48), and those without CAD (clear, N = 29) whose supine bicycle exercise was curtailed because of chest pain, ST segment depression, or pressure-rate product 250. The remainder achieved adequate exercise.

patients in this group had abnormal regional wall motion with exercise (sensitivity of 100%).

In the 13 patients with coronary artery disease who failed to achieve any of the criteria for adequate exercise, the mean ejection fraction was 60.6% at rest increasing to 66.2% during exercise (Table 4). Eight of thirteen had an abnormal global ejection fraction (sensitivity 62%) while only four of thirteen had regional wall-motion abnormalities (sensitivity 31%). The overall sensitivity of RNV in this group was 62% (eight of 13 patients).

The exercise parameters for patients are presented in Table 5. Those with normal coronaries had significantly higher values for heart rate, blood pressure, and PRP than patients with CAD ($p < 0.01$). However, in patients with normal coronaries who failed to achieve adequate exercise there was no difference in these parameters. Within the group with CAD, patients who were inadequately exercised and those on propranolol had significantly lower heart rates and PRPs than those that achieved adequate exercise ($p < 0.05$). Unlike the inadequately exercised group with CAD, all patients with CAD who were on propranolol had an abnormal RNV (62% against 100%, $p < 0.05$). Eight of ten patients with CAD on propranolol achieved adequate exercise (three with chest pains, two with ST-segment depression, three with both). No patient on propranolol achieved a PRP greater than 250. The fact that this group of patients was receiving propranolol at the time of the study suggests that they had clinically more severe disease.

DISCUSSION

Borer et al. (*3,4*) using exercise gated blood-pool imaging demonstrated an abnormal ventricular response to exercise in patients with coronary artery disease at maximal and submaximal exercise levels. Upton et al. (*12*) have emphasized that abnormalities on exercise gated blood-pool imaging could precede ST-segment depression in patients with coronary artery disease. These early studies suggest that exercise radionuclide ventriculography is a sensitive indicator of ventricular dysfunction at both maximal and submaximal levels of stress and has led to widespread use of this technique. In these early studies the patient populations consisted in part of patients with known CAD. The present study demonstrates an excellent sensitivity (85%) for RNV in detecting ventricular dysfunction in patients without prior documented CAD. It also shows that the sensitivity of RNV is significantly lower ($p < 0.02$) in patients who achieved inadequate (62%) as opposed to adequate (94%) levels of exercise.

The criteria for adequate stress with RNV in our laboratory include the development of precordial chest pain, ST segment depression, or PRP >250. Exercise-

TABLE 4. MEAN REST AND EXERCISE EJECTION FRACTIONS, PERCENTAGE OF PATIENTS WITH REGIONAL WALL MOTION ABNORMALITIES (RWMA) AND SENSITIVITY OF CAD DETECTION

	Rest-Exercise (%)	Percent abnormal EF response	Patients with RWMA	RWMA (%)	Sensitivity CAD detection (%)
AD-EX					
(35 Pts)	64.9—60.0*	83	26	74	94
CP (21 Pts)	65.2—60.3*	76	15	71	95
ST↓ (15 Pts)	62.8—55.7†	87	15	100	100
PRP (9 Pts)	63.7—60.5‡	89	6	67	89
Combination					
(10 Pts)	63.7—54.0†	90	10	100	100
INAD-EX					
(13 Pts)	60.6—66.2*	62	4	31	62

* $p < 0.05$.
† $p < 0.02$.
‡ p = NS.

TABLE 5. EXERCISE PARAMETERS

Patients	Heart rate	Blood pressure	P.R.P.	Sensitivity (%)
CAD 48*	111 ± 19	174 ± 20	194 ± 45	85
AD-EX 35†	118 ± 22	175 ± 22	202 ± 48	94
INAD-EX 13‡	101 ± 18	174 ± 16	176 ± 33	62
Propranolol 10	98 ± 14	169 ± 17	166 ± 34	100
				Specificity %
Normal 29	125 ± 18	182 ± 18	227 ± 47	83
AD-EX 16†	132 ± 18	185 ± 20	244 ± 49	88
INAD-EX 13‡	114 ± 11	178 ± 14	202 ± 19	77
Propranolol 3	107 ± 6	175 ± 25	185 ± 16	67

* Coronary artery disease.
† Adequate exercise.
‡ Inadequate exercise.

induced chest pain has been the clinical hallmark of myocardial ischemia. In the present study, 44% of patients with coronary artery disease experienced chest pain during exercise. This percentage is consistent with data in the literature regarding supine exercise. Lichtlen (*13*), in studying the hemodynamic response to supine exercise in patients with coronary artery disease, found that 20 of 39 patients (51%) experienced chest pain with exercise. In the present study, seven patients with normal coronary arteries developed chest pain with exercise. Chest pain developed in one patient with an exercise-induced regional wall-motion abnormality. The cause of chest pain in the remaining patients is unclear. The radionuclide ventricular response clearly separated this group of patients from those with chest pain and coronary artery disease.

Exercise-induced ST segment depression has been the electrocardiographic hallmark of myocardial ischemia (*1,2*). Berger et al. (*14*), using first-pass radionuclide angiography demonstrated 100% sensitivity in detecting ventricular dysfunction in patients with exercise-induced ST segment depression against only a 60% sensitivity in detecting ventricular dysfunction in patients with coronary artery disease but without ST segment depression. In the present study, ST segment depression was present in 31% of patients with coronary artery disease. This is lower than the 50% of patients with ST segment depression in Berger's study. The difference may be accounted for by the transiently higher heart rates that are achieved in first-pass studies, a different lead system, or differences in the patient population. In both studies, however, all patients with coronary artery disease and ST segment depression had an abnormal ventricular response to exercise.

Frishknecht et al. (*15*) using ejection fractions at rest and exercise determined with a dual-probe system found that 17 patients with coronary artery disease had ST segment depression. All 17 had an abnormal ejection-fraction response. Two patients with ST segment depression and normal coronary arteries had a normal radionuclide ventricular ejection-fraction response to exercise. In our study, there was one patient with ST segment depression and normal coronary arteries, who also had a normal ventricular response to exercise. Recent work has emphasized the low sensitivity and specificity of an abnormal ST segment response in detecting patients with CAD (*16,17*). It might be of physiologic interest to apply stress RNV with its high sensitivity and specificity to asymptomatic patients with ST segment depression to determine their ventricular function at the level of ECG abnormality.

On the basis of a PRP greater than 250 during exercise, eight of nine patients with coronary artery disease had an abnormal ventricular response, while 11 of 11 normal patients had a normal response. Factors such as fear of chest pain, sedentary life style, and the supine exercise position itself may cause fatigue or stop patients at a time when they possess normal ventricular reserve. These factors may also account for the high percentage (45%) of "normal" patients who failed to achieve adequate exercise. In the present study the exercise was continued when patients experienced only mild to moderate chest pain or developed ST segment depression. The study was conducted in this manner because chest pain and ST segment depression may be present in patients without CAD. The development of "on-line" EF calculation during RNV will allow assessment of ventricular function during the exercise phase and might serve as a more reliable endpoint with those patients who develop ventricular dysfunction.

Although RNV is a sensitive means of detecting patients with CAD, we emphasize that an abnormal exercise radionuclide study is not specific for patients with CAD. Exercise RNV is primarily a study of ventricular function and functional reserve. Critical narrowing of one or more coronary arteries can cause an abnormal response, but this has also been reported in patients with aortic valvular disease (*18*), myocarditis (*19*), and adriamycin cardiotoxicity (*20*). In the present series the specificity of 83% in detecting coronary artery disease might be considered low. However, three of the five patients who had false-positive studies had a regional myocardial wall-motion abnormality detected by rest and/or exercise contrast ventriculograms. With correct use of stress RNV as a measure of ventricular function instead of an indicator of CAD, these three patients would be considered true positives (abnormal contrast ventriculograms) and the specificity for RNV would increase from 83 to 92% (24 of 26 patients). None of our patients with false-positive studies had evidence of mitral valve prolapse, hypertension, or myocarditis, but an early myopathic condition cannot be excluded.

It is generally accepted that differences in sensitivity between institutions reflect differences in technique and patient population. The present study demonstrates that differences in sensitivity may be related to the adequacy of exercise as well as to differences in populations. If the present sensitivity of CAD detection for adequate (94%) and inadequate (62%) exercise were applied to populations in which 50 and 75% of patients were inadequately exercised, the overall sensitivities would decrease to 78 and 70%, respectively.

In summary, the sensitivity of exercise radionuclide ventriculography is in part dependent upon the adequacy of the exercise. An abnormal exercise ejection-fraction response is not specific for CAD. The results from the present study cannot be extrapolated to patient populations with stenosis between 50 and 70%.

REFERENCES

1. ZOHMAN LR, KATTUS AA: Exercise testing in the diagnosis of coronary artery disease: A perspective. *Am J Cardiol* 40: 243–250, 1977
2. FORTUIN NJ, WEISS JL: Exercise stress testing. *Circulation* 56: 699–712, 1978
3. BORER JS, BACHARACH SL, GREEN MV, et al: Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary-artery disease. *N Engl J Med* 296: 839–844, 1977
4. BORER JS, BACHARACH SL, GREEN MV, et al: Effect of nitroglycerin on exercise-induced abnormalities of left ventricular regional function and ejection fraction in coronary artery disease. Assessment by radionuclide cineangiography in symptomatic and asymptomatic patients. *Circulation* 57: 314–320, 1978
5. BRADY TJ, THRALL JH, CLARE JM, et al: Exercise radionuclide ventriculography: Practical considerations and sensitivity of coronary artery disease detection. *Radiology* 132: 697–702, 1979
6. PAVEL DG, ZIMMER AM, PATTERSON VN: In vivo labeling of red blood cells with ^{99m}TC: A new approach to blood pool visualization. *J Nucl Med* 18: 305–308, 1977
7. HAMILTON GW, WILLIAMS DL, CALDWELL JH: Frame-rate requirements for recording time-activity curves by radionuclide angiography. In *Nuclear Cardiology: Selected Computer Aspects*, Symposium Proceedings. New York, Society of Nuclear Medicine, 1978, pp 75–83
8. BUROW RD, STRAUSS HW, SINGLETON R, et al: Analysis of left ventricular function from multiple grated acquisition cardiac blood pool imaging: Comparison to contrast angiography. *Circulation* 56: 1024–1028, 1977
9. BRADY TJ, LO K, THRALL JH, et al: Exercise radionuclide ejection fraction: Correlation with exercise contrast ventriculography. *Radiology* 132: 703–705, 1979
10. WALTON JA, LO KS, BRYMER JF, et al: Exercise ventriculography: Assessment of the functional significance of coronary artery lesions. *Circulation* 58 (Suppl II): 122, 1978 (abst)
11. BRUCE RA, GEY GO, COOPER MN, et al: Seattle Heart Watch: Initial clinical, circulatory and electrocardiographic responses to maximal exercise. *Am J Cardiol* 33: 459–469, 1974
12. UPTON MT, NEWMAN GE, PORT S, et al: Left ventricular function during two levels of exercise in patients with coronary artery disease. *Am J Cardiol* 43: 433, 1979 (abst)
13. LICHTLEN P: The hemodynamics of clinical ischemic heart disease. *Ann Clin Res* 3: 333–343, 1971
14. BERGER HJ, REDUTO LH, JOHNSTONE DE, et al: Global and regional left ventricular response to bicycle exercise in coronary artery disease. Assessment by quantitative radionuclide angiocardiography. *Am J Med* 66: 13–21, 1979
15. FRISCHKNECKT J, STEELE P, KIRCH D, et al: Effect of exercise on left ventricular ejection fraction in men with coronary artery disease. *Am Heart J* 97: 494–498, 1979
16. REDWOOD DR, BORER JS, EPSTEIN SE: Whither the ST segment during exercise? *Circulation* 54: 703–706, 1976
17. WEINER DA, RYAN TJ, MCCABE CH, et al: Exercise stress testing. Correlations among history of angina, ST-segment response and prevalence of coronary artery disease in the Coronary Artery Surgery Study (CASS). *N Engl J Med* 301: 230–235, 1979
18. BORER JS, BACHARACH SL, GREEN MV, et al: Left ventricular function during exercise before and after aortic valve replacement. *Circulation* 55-56 III-28, 1977 (abst)
19. DAS SV, BRADY TJ, THRALL TH, et al: Evidence of cardiac dysfunction in asymptomatic patients with prior myocarditis. *Circulation* 58: II-24, 1978 (abst)
20. ALEXANDER J, DAINIAK N, BERGER HJ, et al: Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. *N Engl J Med* 300: 278–283, 1979