Myocardial Imaging With Tc-99m Pyrophosphate in Patients on Adriamycin Treatment For Neoplasia

Anna K. Chacko, David H. Gordon, John M. Bennett, Robert E. O'Mara, and George A. Wilson

Strong Memorial Hospital, Rochester, New York

Technetium-99m pyrophosphate was utilized for myocardial imaging in 15 patients on adriamycin treatment for neoplasia. We have noted abnormal accumulation of the pyrophosphate in several patients, particularly in those in whom the so-called poor-risk factors were operative, namely prior radiation, cyclophosphamide therapy, and ischemic heart disease.

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Myocardial uptake of technetium-99m pyrophosphate has been observed in a variety of cardiac conditions including cardiomyopathies, myocardial infarctions, and ventricular aneurysms (*1,2*).

The anthracycline antibiotics, such as adriamycin, are currently being used widely as anticancer agents. Adriamycin has several advantages over other anthracycline antibiotics in that it can be used for the treatment of many more neoplasms (*3,4*). These anthracyclines, however, are known for their tendency to produce serious myocardial damage (*3–11*). This cardiotoxicity, moreover, has been shown to be potentiated by so-called "poor-risk factors," namely prior radiation to the precordium, high doses of cyclophosphamide, and previous heart disease.

On the premise that the myocardium is capable of only a limited type of response to damage, irrespective of cause, we feel that adriamycin-induced cardiac toxicity should result in abnormal Tc-99m pyrophosphate accumulation in the myocardium. To evaluate this, Tc-99m-pyrophosphate myocardial images have been obtained in patients undergoing adriamycin treatment.

METHODS

Myocardial scintiscans were obtained 1 hr following intravenous administration of 15 mCi of Tc-99m pyrophosphate. The precordium was imaged in a variety of projections including the anterior, both anterior obliques, and the left lateral. These multiple projections were essential in order to rule out superficial uptake, such as in the chest wall following surgical procedures. The images were then read by two separate reviewers who had no knowledge of the patients' histories. Among the scans to be reviewed we had included myocardial images from patients with myocardial infarctions. The myocardial uptake of Tc-99m pyrophosphate was graded on a scale of 1 to 4 (*12*). It was noted by both reviewers that myocardial concentration of pyrophosphate was diffuse in the adriamycin patients, unlike the more localized uptake noted in infarctions.

Table 1 presents 15 patients on adriamycin treatment for a variety of neoplasms.

The dosage of adriamycin for these patients varied from 29.1 mg/m^2 to the permissible maximum of 550 mg/m^2. Most of the patients have had radiation to the chest through portals that included the mediastinum. Four patients had documented ischemic heart disease with myocardial infarctions that had occurred 5–10 years before adriamycin therapy. None of these patients had had any evidence of recent myocardial ischemia or infarction. Furthermore, several of them had been on cyclophosphamide therapy either concurrently or before the start of adriamycin. Of the 15 patients imaged, all except Patient 15 were asymptomatic and had no cardiac abnormalities on chest x-ray.

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For reprints contact: George A. Wilson, University of Rochester, Strong Memorial Hospital, Division of Nuclear Medicine, 601 Elmwood Ave., Box 620, Rochester, NY 14642.

TABLE 1. PATIENT DATA

Patient	Age (yr), sex	Tumor	Radiation (rads)	Surgery	C. x-ray	EKG	Cyclophosphamide dosage (mg)	Adriamycin dosage (mg/m²)	Myocardial scan
1	48, M	Transitional cell Ca bladder (1974)	6000 to bladder (1974)	Urethrectomy, prostatectomy	Neg	Old inf. MI*	320	29.41	2+
2	58, F	Lt. infil. ductal Ca bony metastases (1968)	3500 to c. spine; 3300 to t. spine (1975)	Rad. mastec. (1968)	Neg	Neg	4200	33.3	Neg
3	34, F	Lt. infil. ductal Ca (1969)	4500 to chest wall (1972)	Rad mastec. (1972)	Neg	Neg	6300	123.5	Neg
4	42, F	Rt. breast Ca, metas. to skin. Pl. effus. (1975)	—	Rad. mastec., bilat. oophor. (1975)	Neg	Neg	17850	132.2	Neg
5	50, F	Rt. infil. ductal Ca (1974)	—	Simp. mastec. (1974), oophor., on estrogens	Neg	Neg	3050	132.9	2+
6	75, M	Lymphoma III, IV A	1000 for SVC obstruc. (1975)	—	Neg	Old inf. MI	4000	142.1	1+
7	48, F	Nodular sclerosing Hodgkins disease, Stage IV B	—	—	Neg	Old ant. MI	—	161.7	2+
8	29, M	Fibrosarcoma, lt. ilium with metas. to lt. lung	5000 to chest	Local resec.	Neg	Neg	3600	168.2	2+
9	29, M	Osteogenic sarcoma, rt. ilium with pul. metas.	—	Local resec.	Neg	Neg	3600	188.2	Neg
10	62, F	Lt. breast Ca (1969)	6000 to chest	Rad. mastec.	Neg	Neg	7700	203.9	Neg
11	62, F	Poorly differentiated histiocytic lymphoma (abdomen)	—	—	Neg	Neg	7200	323.5	1+
12	58, F	Rt. infil. ductal Ca, bone metastases (1971)	5000 to chest wall (1975)	Rad. mastec. (1971)	Neg	Neg	700	333.3	2+
13	32, F	Rt. infil. ductal Ca, metas. to liver (1974)	4500 to chest wall (1974)	Rad. mastec. (1974)	Neg	Neg	700	417.1	1+
14	29, M	Hodgkins disease stage IV B	—	—	Neg	Neg	—	529.7	Neg
15†	53, F	Lt. intraductal Ca (1969)	6000 to chest wall (1969)	Rad. mastec. (1969)	Cardiac enlarg.	↓ QRS voltage	—	550.0	4+

* MI: myocardial infarction.

† Patient diagnosed as having adriamycin-induced cardiotoxicity.

Patient 15 is a 53-year-old Caucasian woman seen first in 1969 for a mass in her left breast. The mass was diagnosed as an intraductal carcinoma and a left radical mastectomy was performed (1969). In 1974 a supraclavicular swelling was noted and biopsy of this mass showed metastasis from the breast carcinoma. Radiotherapy (4500 rads) was then administered through a portal including supraclavicular lymph nodes and the left internal mammary chain. In early 1976 the patient was started on adriamycin therapy. At this time, her EKG and chest x-ray were both normal. By June of 1976, she had received maximum permissible doses of adriamycin, i.e., 550 mg/m². She was readmitted to the hospital with complaints of shortness of breath and palpitations. An EKG was obtained, and it showed (A) tachy-

cardia with a rate of 110/minute; (B) axis deviation of −30°; (C) poor R-wave progression across the precordial leads; and (D) voltage criteria for left ventricular hypertrophy. Sequential EKGs obtained during this period of hospitalization showed progressive diminution of QRS voltages. A chest x-ray showed marked cardiomegaly. Enzyme studies, including CPK, LDH, and SGOT, were all normal. A clinical diagnosis of adriamycin cardiomyopathy was made. A myocardial scan showed a diffuse (4+) uptake of Tc-99m pyrophosphate throughout the myocardium (Fig. 1).

Patient 8 is a 29-year-old Caucasian man who was diagnosed as having fibrosarcoma of the left ilium. Subsequently he developed metastases to the left lower lung, and received 5000 rads to the chest wall through a portal that included the mediastinum. The only surgical intervention was local resection of the neoplasm. He received 168.2 mg of adriamycin. His myocardial scan performed in the usual manner showed a 2+ positive uptake of Tc-99m pyrophosphate, distributed diffusely throughout the myocardium (Fig. 2).

Patient 7 is a 48-year-old Caucasian woman with a diagnosis of nodular sclerosing Hodgkin's disease, stage IV B. She received a cumulative dose of 161.7 mg/m² of adriamycin. We note that she had had an inferior myocardial infarction several years before the development of the neoplasia. Myocardial scanning was performed, and showed a 2+ positive uptake of Tc-99m pyrophosphate, distributed diffusely throughout the myocardium (Fig. 3).

Figure 4 is the myocardial image from Patient 3, a 34-year-old woman who in 1969 had had a left radical mastectomy following a diagnosis of infiltrating ductal carcinoma. She had received 4500 rads to the chest wall in 1972. Her myocardial scan has been included as an example of a negative uptake. At the time of the scan she had received 123.5 mg/m² of adriamycin and 6300 mg of cyclophosphamide.

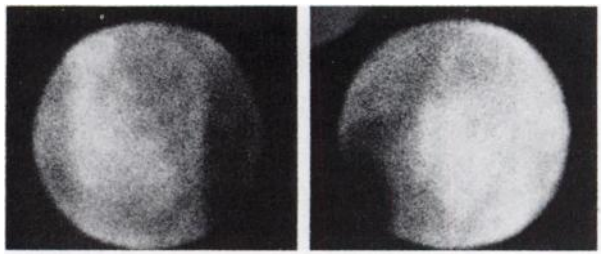

FIG. 1. Patient 15. 4+ myocardial uptake of Tc-99m pyrophosphate seen on anterior and left lateral images.

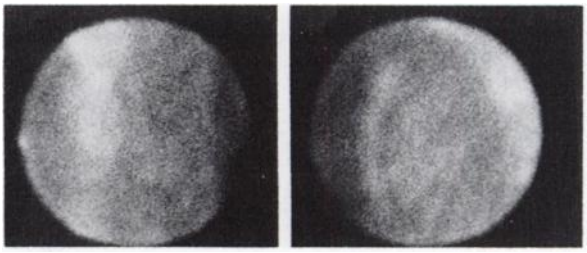

FIG. 2. Patient 8. 2+ myocardial uptake of Tc-99m pyrophosphate seen on anterior and left lateral images.

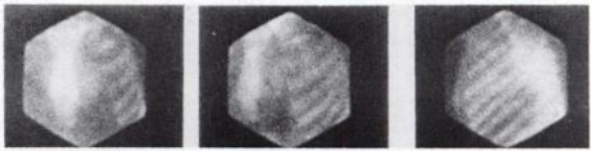

FIG. 3. Patient 7. 2+ myocardial uptake of Tc-99m pyrophosphate seen on anterior, left anterior oblique, and left lateral images.

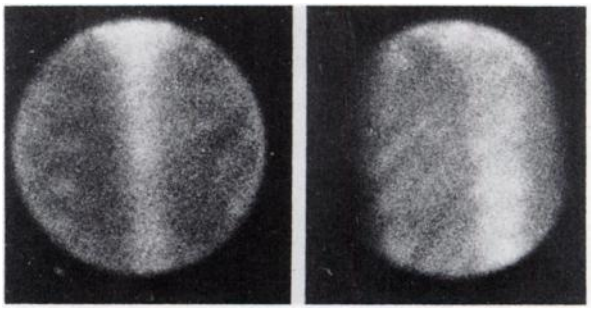

FIG. 4. Patient 3. Anterior and left lateral images show no myocardial uptake of Tc-99m-pyrophosphate.

DISCUSSION

The cardiac toxicity of adriamycin constitutes one of the greatest deterrents to its use. Adriamycin myocardial toxicity is known to be aggravated by several conditions, including radiation therapy, cyclophosphamide therapy, and previous heart disease (*11,13*). Adriamycin itself is known to aggravate radiation-induced heart disease resulting in myocardial damage at lower doses of radiation.

The cardiac toxicity of adriamycin assumes two forms: the acute transient type and the insidious type (*8,9*). The former is acute in onset, occurs in the first few days of therapy, and is reversible. It is not associated with significant morbidity or mortality and is reported to occur in as many as 30% of patients. Manifestations of this variety of toxicity are nonspecific EKG changes, supraventricular arrhythmia, and occasional ventricular premature beats. The insidious type is dose-related, occurs at 1–6 months after treatment, and is seen in patients receiving

levels of adriamycin greater than 500 mg/m², although sometimes it is observed at lower doses (*3–8,11,14–17*). The presentation of this form of adriamycin toxicity is indistinguishable from other forms of cardiomyopathy: the patient shows signs and symptoms of pump failure, diminution of QRS voltage, and poor response to conventional inotropic drugs and mechanical assistance. If enzyme changes occur, they are preterminal and therefore are of little prognostic value.

Damaged myocardium, irrespective of the cause, is capable of only a limited type of response (*7,13*). As such, it is not inconceivable that adriamycin cardiac toxicity would produce abnormal myocardial uptake with currently used myocardial scanning agents such as Tc-99m pyrophosphate. The diagnosis of adriamycin cardiac toxicity has previously been based on nonspecific clinical findings and nonspecific EKG changes and lately changes on echocardiography. Because adriamycin toxicity is reported to be (A) dose related (*3–6,13,14,16*), (B) aggravated by radiation (*11,13*), and (C) potentiated by concurrent or prior cytoxan administration (*11*), an additional mode of diagnosis needs to be developed that will help in the early detection of cardiomyopathy. Treatment could then be curtailed at the earliest possible time.

We feel that the accumulation of Tc-99m pyrophosphate in the myocardium will occur at the stage when the damage is still at the microscopic level rather than at the gross functional level. Because adriamycin cardiomyopathy bears a uniformly poor prognosis, a technique to document myocardial abnormalities at a stage when they are remediable would have wide clinical application. Echocardiography—the latest addition to the clinician's armamentarium for diagnosis of cardiomyopathy—suffers from an inherent disadvantage in that it becomes informative only when gross functional abnormality is present. Myocardial scanning may prove to be a valuable diagnostic tool in monitoring the adverse effects of the anthracycline antibiotics in patients who are receiving them.

We are currently investigating the use of myocardial scanning for the early detection of adriamycin myocardial toxicity both in patients and in experimental animals. We hope to be able to evaluate the potentiating effects of radiation therapy, cyclophosphamide therapy, and previous heart disease on adriamycin-induced cardiomyopathy.

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