

Indium-111-Antimyosin and Iodine-123-MIBG Studies in Early Assessment of Doxorubicin Cardiotoxicity

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Detection of myocyte cell damage with ^{111}In -antimyosin and impairment of adrenergic neuron function with [^{123}I]MIBG during doxorubicin administration may provide early identification of patients at risk of significant functional impairment. **Methods:** We studied 36 cancer patients who underwent chemotherapy, including doxorubicin, to assess [^{123}I]MIBG and ^{111}In -antimyosin uptake in the course of doxorubicin administration. MIBG scans, antimyosin scans and ejection fraction measurements were performed before chemotherapy, at intermediate cumulative doses and at maximal cumulative doses of doxorubicin. MIBG uptake was quantified by a heart-to-mediastinum ratio and antimyosin uptake was quantified by a heart-to-lung ratio. **Results:** All patients had absent antimyosin uptake (mean ratio 1.40 ± 0.06) with normal MIBG uptake (ratio 1.85 ± 0.29) before chemotherapy; ejection fraction was $61\% \pm 8\%$. With a 240–300 mg/m^2 dose of doxorubicin, an increase in antimyosin uptake was observed with a ratio of 1.85 ± 0.2 ($p < 0.01$), whereas a similar degree of MIBG uptake was observed (mean ratio of 1.80 ± 0.2 , $p = \text{ns}$); ejection fraction was $59\% \pm 5\%$ ($p = \text{ns}$). At 420–600 mg/m^2 , increased antimyosin uptake was observed with a ratio of 2.02 ± 0.3 ($p < 0.01$), and a decrease in MIBG uptake was also observed (mean ratio of 1.76 ± 0.2 , $p < 0.05$); ejection fraction was $52\% \pm 8\%$ ($p < 0.05$). Patients with more intense antimyosin uptake at intermediate doses tended to be those with more severe functional impairment at maximal cumulative doses. **Conclusion:** At cumulative doses of 420–600 mg/m^2 , antimyosin and MIBG studies detect cell damage and impaired adrenergic neuron activity in patients with maintained or slightly decreased ejection fraction.

Key Words: indium-111-antimyosin; iodine-123-metaiodobenzylguanidine; doxorubicin cardiotoxicity; myocardial damage; myocardial sympathetic innervation

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Cardiotoxicity is the most deleterious effect of doxorubicin. Its appearance may produce irreversible congestive heart failure, limiting the total cumulative dose achievable (1–4). Detection of cardiotoxicity is therefore crucial in the

management of these patients, with serial ejection fraction measurements being the standard method to guide doxorubicin administration during chemotherapy. Although left ventricular ejection fraction (LVEF) at rest is used by most oncologists to guide doxorubicin therapy, several reports have shown that it may correlate poorly with endomyocardial biopsy grades, suggesting limited sensitivity of ejection fraction measurements to early myocardial damage (1,2,5). Right ventricular endomyocardial biopsy has also been proposed to assess myocardial cell damage during doxorubicin administration. The invasiveness and associated complications of biopsy, however, limit its use in clinical routine. Therefore, a more sensitive and noninvasive method capable of identifying patients at risk of significant ejection fraction deterioration during chemotherapy would be useful, because patients at risk could benefit from changes in the administration schedule to avoid significant functional impairment, or further doxorubicin doses could be administered to those patients who might respond to additional treatment. Recently, assessment of myocardial damage with ^{111}In -antimyosin has been proposed as a more sensitive method for early detection of doxorubicin cardiotoxicity (6–8). In addition, animal studies suggest that assessment of myocardial sympathetic innervation impairment with radioiodinated metaiodobenzylguanidine (MIBG) could also be used for early detection of doxorubicin cardiotoxicity (9,10).

Indium-111-antimyosin antibody studies allow noninvasive detection of myocardial damage in vivo. Binding of this antibody to intracellular myosin takes place only when sarcolemmal disruption occurs and the cell is irreversibly damaged (11). Antimyosin studies have been shown to be sensitive in the detection of myocyte cell damage in a variety of conditions (12–14). We have recently shown that the morphologic damage in the myocytes present in doxorubicin cardiotoxicity can be detected by antimyosin scans (6), that intensity of antimyosin uptake relates to the cumulative dose of doxorubicin (7) and that antimyosin uptake precedes ejection fraction deterioration (7,8).

MIBG behaves similarly to norepinephrine and is taken up by myocardial sympathetic nerves (15–17). Several studies have shown that variations in myocardial MIBG uptake reflect changes in myocardial adrenergic neuron integrity

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and function (18–20). Recently, MIBG studies have been proposed to assess adrenergic innervation impairment due to doxorubicin cardiotoxicity. Animal studies have shown that in adriamycin-induced cardiomyopathy abnormal adrenergic neuron activity can be detected by MIBG. Decreased MIBG uptake has been observed in adriamycin treated rats with limited morphological damage (vacuolar degeneration of the myocytes) (9). In these animal studies, decreased MIBG uptake preceded ejection fraction deterioration (10).

This study was undertaken to assess myocyte cell damage with ^{111}In -antimyosin and impairment of adrenergic neuron function with [^{123}I]MIBG during doxorubicin administration in cancer patients.

METHODS

We studied 36 consecutive patients with sarcomas eligible for treatment including doxorubicin: soft-tissue sarcoma (24 patients) and osteosarcoma (12 patients). There were 21 men and 15 women, aged 16–75 yr (mean age 38 yr). None of the patients had a history of neuropathy, hypertension, previous cardiac disease or had received previous chemotherapy or mediastinal radiotherapy. None of the patients were taking medication which might be expected to interfere with myocardial MIBG uptake. All patients had adequate hepatic and renal function, none had evidence of central nervous system, mediastinal or cardiac metastases. Regimens utilizing doxorubicin were based on a chemotherapeutic protocol (including dacarbazine, cyclophosphamide and vincristine) and disease status. Doxorubicin was administered every 3–4 wk at a dose of 60 mg/m². Informed consent was obtained from all patients.

Iodine-123-MIBG, ^{111}In -antimyosin studies and ejection fraction measurements were performed within the same week before chemotherapy at intermediate cumulative doses (240–300 mg/m²) and at maximal cumulative doses (420–600 mg/m², depending on chemotherapeutic protocol) of doxorubicin. Iodine-123-MIBG studies were performed first, followed by ^{111}In -antimyosin studies to avoid significant cross-talk from the ^{111}In to ^{123}I channels. All studies in the chemotherapy course were performed 2 wk after previous doxorubicin administration.

Antimyosin Studies

R11-D10-Fab-DTPA (0.5 mg) labeled with 2 mCi ^{111}In was administered by slow intravenous injection. Planar scans were obtained 48 hr later using a large field of view camera linked to a dedicated computer with a medium-energy collimator. A 20% window was centered on both peaks of ^{111}In and a preset acquisition time of 10 min was used. Scans were stored in 128 × 128 frames for subsequent analysis. A quantitative method to measure the intensity of antimyosin uptake was then applied (21). This consisted of drawing a region of interest (ROI) on the heart and regions on the lungs on the anterior view of the thorax. A heart-to-lung ratio (HLR) was obtained dividing average counts per pixel in the heart by average counts per pixel in the lungs. Intra- and interobserver variability of HLR have been previously assessed (21). A cutoff point of >1.55 (normal value 1.46 ± 0.04 + 2 s.d.) was used to define abnormal studies (6–8,13,14).

MIBG Studies

Five millicuries [^{123}I]MIBG were administered intravenously. The thyroid was blocked for ^{123}I uptake by oral administration of

40 mg potassium perchlorate 2 hr before and 6 hr after [^{123}I]MIBG administration. Planar images of the heart were obtained 15 min and 4 hr after MIBG administration with the same equipment. A 20% window was used centered at 159 keV. Anterior and oblique views of the thorax were stored in 128 × 128 frames. MIBG uptake was quantified by calculating a heart-to-mediastinum ratio (HMR) (18,20) and drawing ROIs over the mediastinum and the myocardium on the anterior views of the thorax. Care was taken to exclude the lungs or liver from the myocardial region and to exclude large vessels and lung from the mediastinal region. To obtain the HMR, average counts per pixel in the myocardium were divided by average counts per pixel in the mediastinum. Intraobserver variability of HMR, when reviewing studies randomly at different times, was <2.3%; interobserver variability (two observers) was <5%.

Gated Blood-Pool Scans

After red blood cell labeling with 25 mCi $^{99\text{m}}\text{Tc}$, gated blood-pool scans were acquired with the patients supine using the same gamma camera in the LAO 30°–50° projection and 5°–10° caudal tilt to provide the best separation between both ventricles and atria. The cardiac cycle was separated into 30 64 × 64 frames, with a minimum of 300,000 counts collected in each frame. Data were stored on magnetic disk for subsequent analysis. Left ventricular ejection fraction was measured using a semiautomatic edge detection and counts technique with a varying ROI. Fourier-phase and amplitude images were generated to help trace ROIs.

Statistical Analysis

Results are expressed as mean ± s.d. of mean with nonparametric analysis of groups using the Mann-Whitney and Wilcoxon tests. Regression analysis was used to assess correlation between variables. The statistical package for social sciences (SPSS/PC) was used to measure all calculations.

RESULTS

Before Chemotherapy

All patients had normal antimyosin and MIBG scans before chemotherapy. Visual assessment of the antimyosin scans showed absent myocardial antimyosin uptake, with a mean HLR of 1.40 ± 0.06 (range 1.32–1.50) at 48 hr postinjection. Visual assessment of the MIBG scans showed normal myocardial MIBG accumulation, with a mean HMR of 1.91 ± 0.30 at 15 min postinjection and of 1.85 ± 0.29 at 4 hr (range 1.31 to 2.62) (*p* = ns). Mean LVEF was 61% ± 8% (range 48% to 78%). (Table 1, Fig. 1).

Intermediate Cumulative Doses

At the 240–300 mg/m² dose of doxorubicin, visual assessment of the antimyosin scans showed myocardial antimyosin uptake in 34 of 36 patients (94%), mild antimyosin uptake was present in 7, moderate in 24 and intense in 3 patients. Mean HLR was 1.85 ± 0.2 (range 1.46 to 2.2) (*p* < 0.01). Visual assessment of the MIBG scans showed mild decrease in myocardial MIBG uptake in 9 of 36 patients (25%), with a mean HMR of 1.80 ± 0.2 (range 1.30–2.57) 4 hr postinjection (*p* = ns). Mean LVEF was 59% ± 5% (range 53% to 71%) (*p* = ns). (Table 1, Fig. 1). None of the patients had a decrease in LVEF ≥10%.

TABLE 1
Mean \pm s.d. (range) Values of LVEF and of Antimyosin and MIBG Uptake

	Before chemotherapy	240-300 mg/m ²	420-600 mg/m ²
LVEF	61% \pm 8% (48-78)	59% \pm 5% (53-71)	52 \pm 8 (38-70)*
Antimyosin	1.40 \pm 0.06 (1.32-1.50)	1.85 \pm 0.20 (1.46-2.20)**	2.02 \pm 0.30 (1.63-2.80)**
MIBG	1.85 \pm 0.29 (1.31-2.62)	1.80 \pm 0.20 (1.30-2.57)	1.76 \pm 0.20 (1.20-2.50)*

*p < 0.05; **p < 0.001.

Maximal Cumulative Doses

At the 420-600 mg/m² dose of doxorubicin, visual assessment of the antimyosin scans showed increased myocardial antimyosin uptake in all patients: mild antimyosin uptake was present in 3, moderate in 22 and intense in 11 patients. The mean HLR was 2.02 \pm 0.3 (range 1.63 to 2.80) (p < 0.01). Visual assessment of the MIBG scans showed a decrease in myocardial MIBG uptake in 19 of 36 patients (52%), mild decrease was observed in 12 and marked decrease in 7 patients. The mean HMR 4 hr postinjection was 1.76 \pm 0.2 (range 1.20 to 2.50) (p < 0.05). (Table 1, Figs. 1, 2). Differences in HMR 15 min and 4 hr before chemotherapy, at intermediate and high cumulative doses were nonsignificant. Mean LVEF was 52% \pm 8% (range 38% to 70%) (p < 0.05). Nine patients had a decrease in LVEF \geq 10% and four had mild symptoms of congestive heart failure (third heart sound gallop and/or rales in less than half the lung fields) (Table 2, Fig. 3).

DISCUSSION

The appearance of cardiomyopathy is the most serious toxic effect of doxorubicin, and the one that limits its use in the treatment of lymphoma, leukemia and several solid tumors. After reaching a total cumulative dose of 500 mg/m², additional treatment with doxorubicin produces a rapidly increasing incidence of clinically significant cardiomyopathy (1), although congestive heart failure may occur with lesser doses. Ceasing the administration of doxorubi-

cin at a fix cumulative dose is a commonly used approach that has important clinical implications that cannot be overlooked. Several studies suggest that those patients in remission at 450-550 mg/m² could have their remission time prolonged with additional administration of doxorubicin. Patients who would tolerate higher cumulative doses could benefit from additional doxorubicin administration in terms of tumoricidal effect or duration of clinical response.

Detecting patients at risk of cardiomyopathy before ejection fraction deteriorates could be of interest, since those patients could benefit from alternative administration regimens to avoid or delay significant functional impairment. Left ventricular ejection fraction measurements seem not to be sensitive enough to detect patients at risk of significant cardiotoxicity at an early stage (2,3,5). This is in keeping with the concept of the need for a certain critical mass of cell damage before functional impairment can be detected by conventional methods (2,3). Our use of noninvasive methods in this study also support this concept, since all patients who presented with a decrease in ejection fraction \geq 10% at a dose of 420-600 mg/m² had intense diffuse antimyosin uptake at intermediate doses with a HLR \geq 1.90. Similar results were reported by Valdés Olmos et al. (22), who found intense antimyosin uptake with a HLR \geq 1.87 in the majority of patients who developed congestive heart failure with additional anthracycline administration.

Small dimensions of antimyosin Fab (35 \times 65 Å) enable it to enter the membrane gaps created by complement membrane attack complexes or by inflammatory reactions (23). The disruption of sarcolemmal continuity may subsequently result in myocyte necrosis. The present study, performed in patients without previous risk factors, again shows that the intensity of antimyosin uptake relates to the cumulative dose of doxorubicin, and that intense antimyosin uptake precedes significant ejection fraction deterioration. When a certain degree of myocardial cell damage is reached, as shown by the high HLR in antimyosin studies, significant decreases in ejection fraction and symptoms of overt heart failure are more likely to occur with additional doxorubicin administration.

None of the patients who developed significant functional impairment at high cumulative doses had significant decreases in ejection fraction (decrease \geq 10%) at intermediate cumulative doses. It is possible that exercise ejection fraction measurements at intermediate cumulative doses (24) or detailed assessment of diastolic function parame-

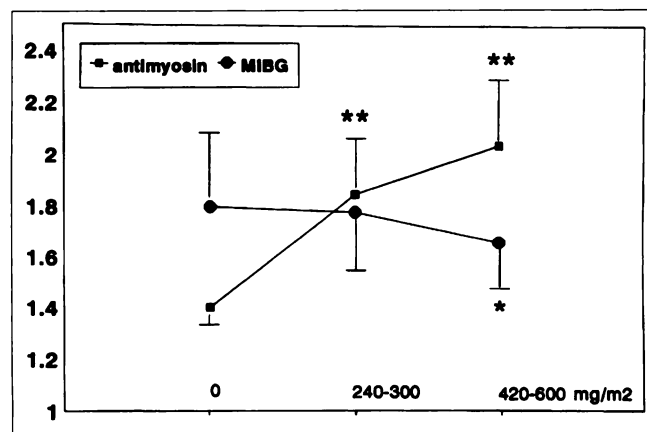


FIGURE 1. Evolution of heart-to-lung and heart-to-mediastinum ratios in antimyosin and MIBG studies during doxorubicin administration.

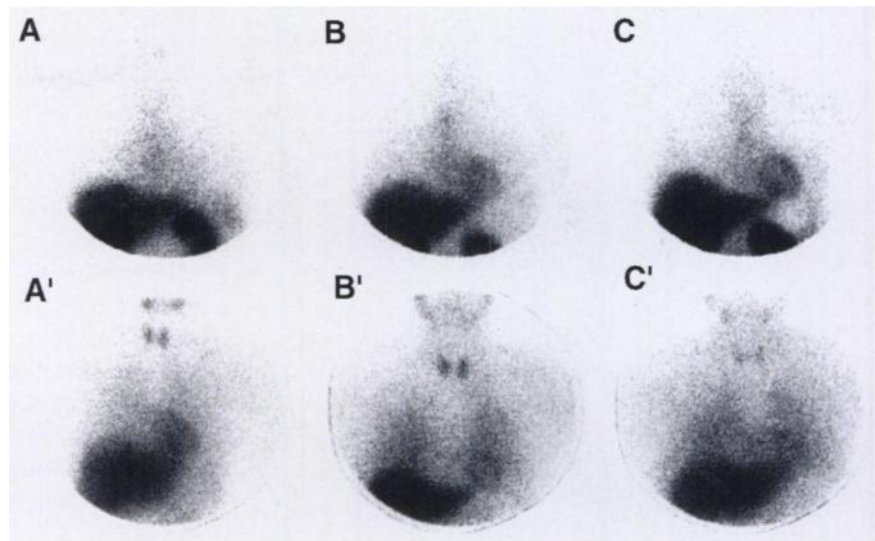


FIGURE 2. Sequential antimyosin (A, B, C) and MIBG (A', B', C') studies before chemotherapy (A, A') at 240–300 mg/m² (B, B') and at 420–600 mg/m² of doxorubicin. There is a pattern of increasing myocardial antimyosin uptake with decreasing myocardial MIBG uptake.

ters could have revealed significant cardiotoxicity in these patients (25). Exercise monitoring of these patients is impractical, however, since most of them are deconditioned and debilitated and are unable to undergo repeat stress testing at adequate exercise levels.

Many studies have demonstrated the affinity of MIBG for the adrenal medulla and adrenergic nerves, resulting in physiological cardiac MIBG uptake in humans (15). Images of the heart obtained 4 hr after MIBG administration reflect cardiac neuronal activity, since at that time a plateau value of 50% is reached in intravesicular MIBG concentration (26). Normal myocardial visualization with MIBG is usually observed in untreated oncologic patients without adrenergic hyperfunction due to excess circulating catecholamines from the tumor (i.e., pheochromocytomas) (27,28). Myocardial MIBG accumulation can be neuronal and non-neuronal, as shown in different animal models (20,26). Recent studies performed in transplanted hearts, however, have shown that the non-neuronal uptake mechanism is not significant in human myocardium, and there-

fore should not influence the results obtained in human studies (20).

Animal studies have shown that abnormal adrenergic neuron activity can be detected by MIBG studies in adriamycin-induced cardiomyopathy (9). Decreased myocardial MIBG uptake has been observed in adriamycin treated rats with limited morphological damage (vacuolar degeneration of the myocytes). In these animal studies, decreased myocardial MIBG uptake preceded ejection fraction deterioration (10). Valdés Olmos et al. reported decreased myocardial MIBG uptake in six patients with severely decrease ejection fraction after doxorubicin administration (29). Correlation with parameters derived from radionuclide angiocardiology suggested a global process of myocardial adrenergic derangement. Wakasugi et al. have shown reduced myocardial tissue bound norepinephrine and MIBG in adriamycin-treated rats (10). In that study, MIBG uptake revealed a dose-dependent decline which could be due to excessive compensatory hyperadrenergic washout from the myocardium or to direct adrenergic neuron damage. Hy-

TABLE 2
LVEF, Antimyosin and MIBG Uptake Values in Patients with a Decrease in Ejection Fraction \geq 10%

Patient no.	Before chemotherapy			240–300 mg/m ²			420–600 mg/m ²		
	LVEF	Antimyosin	MIBG	LVEF	Antimyosin	MIBG	LVEF	Antimyosin	MIBG
1	63	1.40	1.76	60	1.94	1.75	41*	1.96	1.50
2	50	1.44	2.02	46	2.02	1.90	38*	2.12	1.68
3	70	1.32	1.66	65	1.95	1.64	53	2.10	1.70
4	76	1.35	2.00	70	1.86	1.95	58	1.92	1.75
5	69	1.40	2.40	69	1.90	2.35	54	1.98	2.00
6	78	1.45	1.80	70	1.91	1.69	61	2.05	1.54
7	59	1.36	1.73	60	2.00	1.65	45*	2.10	1.60
8	55	1.38	1.90	53	2.20	1.72	42*	2.73	1.63
9	60	1.42	1.88	62	1.92	1.76	54	2.00	1.69
Mean \pm s.d.	64 \pm 9	1.39 \pm 0.04	1.90 \pm 0.22	61 \pm 8	1.96 \pm 0.10	1.82 \pm 0.22	49 \pm 8	2.10 \pm 0.24	1.67 \pm 0.14

*Patients who presented with symptoms of congestive heart failure.

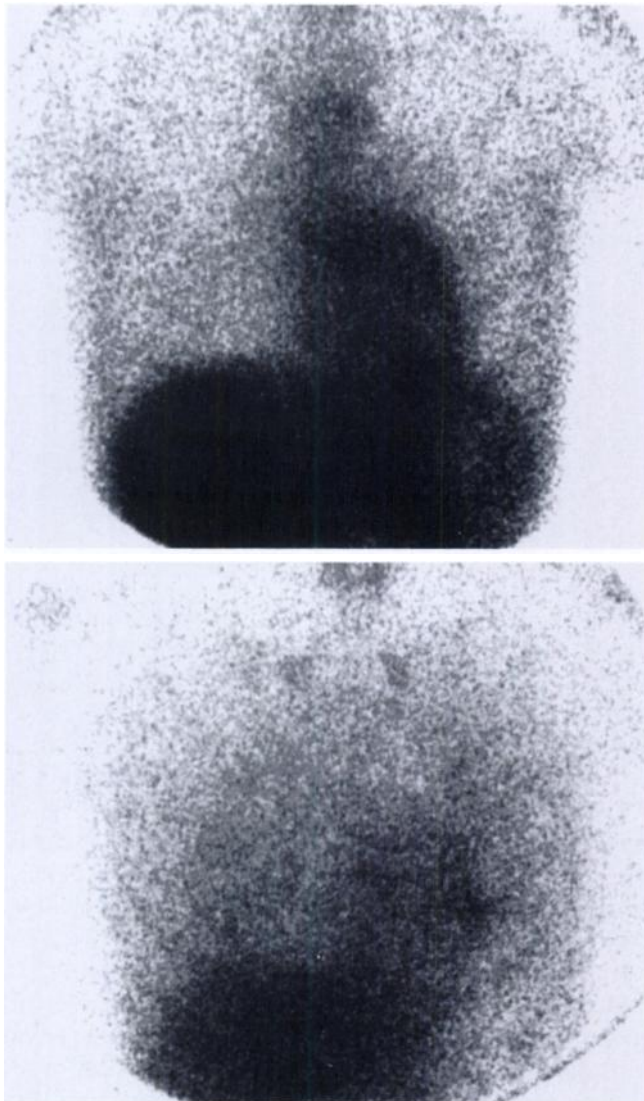


FIGURE 3. Antimyosin (top) and MIBG (bottom) scans at a dose of 480 mg/m² of doxorubicin in a patient who presented with symptoms of congestive heart failure. There is intense myocardial antimyosin uptake and a marked decrease in myocardial MIBG uptake.

peradrenergism seemed unlikely since myocardial norepinephrine did not decline as plasma norepinephrine levels rose with increasing dose. This suggested specific adrenergic neuron toxicity rather than a nonspecific response to an impairment in ventricular function.

Our observation of some decrease in myocardial MIBG uptake regardless of the functional status also suggests a specific effect. Progressive myocyte necrosis during doxorubicin cardiotoxicity could be associated with cardiac neuroadrenergic tissue necrosis. In fact, the clinical course of doxorubicin cardiotoxicity suggests altered neuroendocrine physiology. This is supported by the observation of a decrease in beta-adrenergic responsiveness and decreased myocardial catecholamine stores with increased plasma catecholamines (24).

Results of the present series show that the decrease in myocardial MIBG accumulation parallels the evolution of

ejection fraction. At intermediate cumulative doses of 240–300 mg/m², 25% of patients presented with some decrease in MIBG uptake, although HMR values compared to those obtained at baseline did not reach a significant difference. At maximal cumulative doses, and considering the whole group of patients, there was a significant decrease in MIBG uptake consistent with impaired cardiac adrenergic activity. In our series, a clear relation between more decreased myocardial MIBG uptake and more severe functional impairment could not be obtained. Differences between our results and the results of previously published animal studies using a rat model (9,10) could be explained by the differences in the adrenergic innervation and patterns of catecholamine uptake and storage by the heart in different species. Moderate to marked decrease in myocardial MIBG uptake at high cumulative doses, however, was observed in all but one patient with decreased ejection fraction $\geq 10\%$. Interestingly, some of our patients had relatively low HMR values at baseline; these patients were over 60 yr of age. We previously observed an effect of age on myocardial MIBG uptake (30), which may explain the low HMR values in patients without known disease or medication and could account for the decreased uptake. Recently, Takeishi et al. (31) used [¹²³I]BMIPP to identify anthracycline cardiotoxicity. The assessment of metabolic changes in the myocardium using labeled fatty acids may provide further insight into the mechanisms of cardiotoxicity.

It is difficult to anticipate if early detection of cardiotoxicity with noninvasive methods such as antimyosin or MIBG studies may influence management strategies in the future. Although serial resting LVEF measurements will probably remain the method of choice to monitor cardiotoxicity, it is possible that using a more sensitive test drug administration could be individually tailored to meet specific clinical needs (32). A complementary approach with functional assessment, together with an assessment of myocardial damage or adrenergic innervation status, could be helpful for individual management of patients with previous risk factors or of patients who are potential candidates for future repeat doxorubicin administration. Furthermore, an unexpectedly high incidence of late cardiac abnormalities has been reported in patients recovering from the disease who were studied during long-term follow-up (33). It is possible that early detection of cardiotoxicity in these circumstances could prompt changes in the pharmaceutical administration schedule which could prevent these late undesirable cardiac effects of doxorubicin therapy.

CONCLUSION

Myocyte cell damage due to doxorubicin cardiotoxicity precedes ejection fraction deterioration and can be detected by antimyosin studies at intermediate cumulative doses of 240–300 mg/m² during chemotherapy. Impaired cardiac adrenergic neuron function parallels ejection fraction deterioration and can be detected with MIBG studies at higher cumulative doses. At cumulative doses of 420–

600 mg/m², antimyosin and MIBG studies detect cell damage and impaired adrenergic neuron activity in patients with maintained or slightly decreased ejection fraction.

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