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Noninvasive identification of anthracycline cardiotoxicity: Comparison of ^{123}I-MIBG and ^{123}I-BMIPP imaging

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To test the feasibility of myocardial ^{123}I-MIBG and ^{123}I-BMIPP imaging for the early detection of anthracycline cardiotoxicity, 13 patients who had received anthracycline anticancer chemotherapeutic agents were studied. Two-dimensional echocardiography and myocardial imaging with both ^{123}I-MIBG and ^{123}I-BMIPP were performed in 13 patients treated with anthracycline (group A) and 10 normal control subjects (group C). Anterior myocardial images were obtained 15 minutes and 3 hours after the injection of isotopes. The heart-to-mediastinum ratio (H/M ratio) was used to quantify cardiac ^{123}I-MIBG and ^{123}I-BMIPP uptake. The left ventricular shortening fraction (%SF) and the ratio of peak mitral flow velocity in early diastole to that at the time of atrial systole (E/A ratio) were measured by echocardiography. The H/M ratio of ^{123}I-MIBG was lower in group A than in group C (1.5 ± 0.2 vs. 1.9 ± 0.2, $p < 0.01$). The patients in group A had faster clearance of ^{123}I-MIBG from the myocardium than those in group C ($27 \pm 10\%$ vs. $22 \pm 4\%$, $p < 0.05$). However, the H/M ratio and clearance of ^{123}I-BMIPP were similar between the two groups (H/M ratio: 2.1 ± 0.2 vs. 2.0 ± 0.2, clearance: $24 \pm 6\%$ vs. $26 \pm 6\%$). The %SF ($37 \pm 8\%$ vs. $36 \pm 7\%$) and E/A ratio (1.4 ± 0.4 vs. 1.6 ± 0.3) were comparable in groups A and C.

The present findings indicated that myocardial imaging with ^{123}I-MIBG could detect myocardial damage in patients treated with anthracycline in the early stage when cardiac systolic and diastolic function was still preserved. Early detection of anthracycline cardiotoxicity by ^{123}I-MIBG would reduce the incidence and severity of heart failure.

Key words: ^{123}I-MIBG, ^{123}I-BMIPP, doxorubicin cardiotoxicity

INTRODUCTION

ANTHRACYCLINE CLASS CHEMOTHERAPEUTIC AGENTS are effective in treating hematological malignancies as well as solid tumors. Its administration, however, is limited by a dose-related cardiotoxicity that may lead to congestive heart failure, which is frequently fatal.[1-3] Although numerous noninvasive methods, including electrocardiography,[4] chest x-ray, echocardiography,[5,6] and radionuclide ventriculography,[7-10] have been used to detect anthracycline-induced cardiotoxicity, they had only limited value in predicting cardiotoxicity and cardiac dysfunction. Evident congestive heart failure is a late manifestation of myocardial damage, and it has been established that a large proportion of patients with normal cardiac function are at risk of congestive heart failure.[11] Histopathologic changes precede clinical cardiotoxicity, and endocardial biopsy is now considered the most reliable method for detecting anthracycline-induced myocardial damage.[12] However, endocardial biopsy is invasive and is not acceptable for the repeated examination. Therefore, a practical noninvasive method for monitoring anthracycline-induced myocardial damage has long been desired.

The development of radioiodinated metaiodobenzylguanidine (MIBG), an analog of norepinephrine, has allowed a study of the cardiac adrenergic nervous system *in vivo*.[13] The MIBG kinetics in the myocardium has been shown to reflect cardiac adrenergic neuron integrity and

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function.[14,15] Recently, Wakasugi et al. have reported that ^{125}I-MIBG scintigraphy is useful for the detection of adriamycin cardiomyopathy in rats.[16,17] However, the application of this radiopharmaceutical has not been confirmed in clinical trials.

Iodine-123 beta-methyl-iodophenyl-pentadecanoic acid (^{123}I-BMIPP) has been developed as a tracer for myocardial fatty acid metabolism.[18,19] Fatty acids are known to account for more than 90% of myocardial energy requirements at rest under normal fasting aerobic conditions.[20] Wakasugi et al. have recently shown that myocardial substrate utilization, including fatty acids, is changed in adriamycin-induced cardiomyopathic rats.[21] However, metabolic states of the myocardium in patients treated with anthracycline have not been rigorously examined.

The aim of the present study was to determine whether myocardial imaging with ^{123}I-MIBG and ^{123}I-BMIPP could identify the myocardial damage in patients treated with anthracycline anticancer chemotherapeutic agents.

Table 1 Characteristics of anthracycline patients

No.	Sex	Age	Cancer type	Drugs (total dose)
1	f	55	AML	DNR 500 mg
2	f	44	AML	DNR 360 mg
3	m	23	ALL	DXR 250 mg
4	m	39	AML	DNR 360 mg, ACR 540 mg
5	f	46	AML	DNR 500 mg, ACR 220 mg
6	m	58	AML	ACR 1,260 mg
7	f	64	MM	DXR 96 mg
8	m	27	ML	DXR 350 mg
9	m	70	ML	DXR 330 mg
10	m	71	ML	DXR 120 mg
11	f	63	ML	DXR 320 mg
12	m	64	ML	DXR 240 mg
13	m	64	ML	DXR 380 mg

m: male, f: female, AML: acute myelocytic leukemia, ALL: acute lymphocytic leukemia, MM: multiple myeloma, ML: malignant lymphoma, DNR: daunorubicin, ACR: aclarubicin, DXR: doxorubicin

MATERIALS AND METHODS

Subjects

Thirteen patients with malignant neoplasms who had been previously treated with anthracycline anticancer agents were studied. These were 8 males and 5 females aged 23 to 71 years (mean 53 years). The control group was composed of 10 normal subjects (6 male and 4 female) aged 28 to 66 years (mean 45 years). The etiology of the primary neoplasms and cumulative doses of anthracycline agents in treated patients are shown in Table 1. Because the objective was to evaluate asymptomatic anthracycline treated patients, patients with congenital heart disease, heart failure and arrhythmias were excluded. The time elapsed since the last dose of anthracycline therapy ranged from 4 to 12 weeks (mean 5.6 week).

Myocardial imaging of ^{123}I-MIBG and ^{123}I-BMIPP

Study protocol: Myocardial imaging with ^{123}I-MIBG and echocardiography were performed on the same day in all subjects. Myocardial imaging with ^{123}I-BMIPP was performed within one week following the ^{123}I-MIBG studies (3 to 7 days). All patients were not received the anticancer chemotherapeutic agents between the two imaging.

Image acquisition: After an overnight fast, a dose of 111 MBq of ^{123}I-MIBG or ^{123}I-BMIPP was administered intravenously with the patients in the resting supine position. Anterior projection images were obtained 15 minutes and 3 hours after injection. A large field-of-view gamma camera (Siemens, ZLC-7500 DIGITRAC) equipped with a parallel hole, high resolution collimator was used. Each image accumulated for 10 minutes. The data were stored on a 256 × 256 matrix. Data processing was performed by a nuclear medicine computer (Shimadzu, Scintipac 700)

Data analysis: Square regions of interest (12 × 12 pixels in size) were defined for areas of the left ventricular myocardium with the peak count density. Another ROI (20 × 20 pixels in size) was placed over the upper mediastinum area. The heart-to-mediastinum ratio (H/M ratio) was calculated to quantify cardiac ^{123}I-MIBG or ^{123}I-BMIPP uptake as a fraction of the mean counts per pixel in the myocardium divided by those in the mediastinum.[22,23] The ^{123}I-MIBG or ^{123}I-BMIPP clearance from the myocardium was calculated as follows: (initial activity − delayed activity) / initial activity × 100.

Echocardiography

Echocardiographic recording: The heart was imaged with an SSD-870, Aloka echocardiography by an experienced cardiologist. M-mode echocardiograms of the left ventricle from the parasternal long axis were recorded in the standard manner. Then the subjects were placed in the left lateral decubitus position. The transducer was oriented to obtain an apical four-chamber view that provided good visualization of the mitral anulus and leaflets. Doppler examination of mitral flow velocity was performed with the range-gated pulsed Doppler technique. The cursor line of the ultrasound beam was positioned as nearly parallel to the flow as possible. The Doppler sample volume was placed at the level of the mitral anulus.

Echocardiographic measurements: Left ventricular dimensions at end-diastole (LVDed) and end-systole (LVDes) were measured in cm according to the American Society of Echocardiography criteria with an average of 3 to 5 cycles.[24] The left ventricular shortening fraction (%SF) was calculated as follows: (LVDed − LVDes) / LVDed × 100. Mitral peak flow velocities were measured in early diastole (peak E, in cm/second) and at the time of

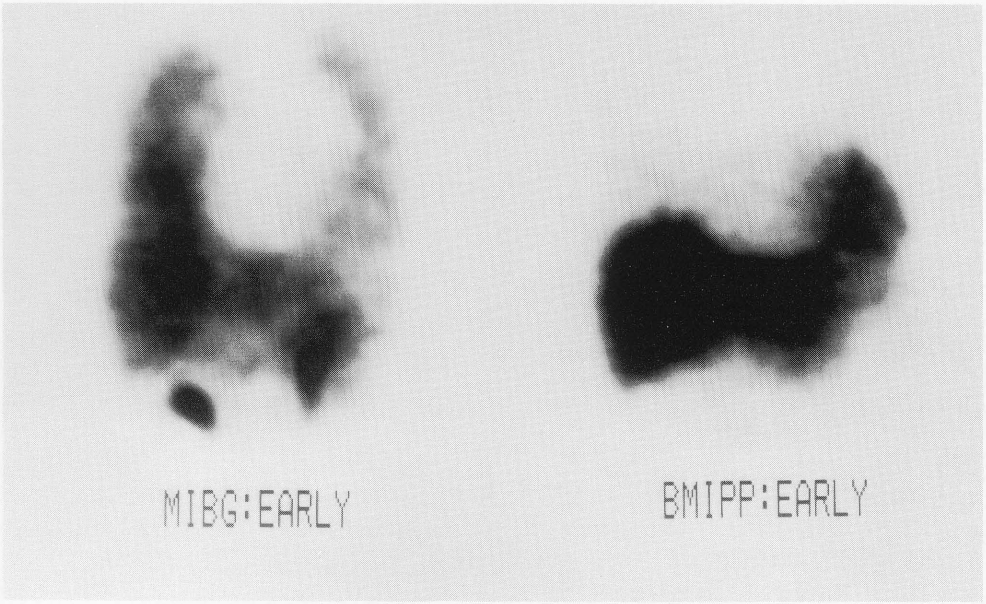

Fig. 1 Initial anterior images of a patient treated with doxorubicin. In the ^{123}I-MIBG image (left panel), the left ventricular myocardium was not visible, indicating a marked reduction in cardiac ^{123}I-MIBG uptake. The left ventricular myocardium was clearly visible in the ^{123}I-BMIPP image (right panel).

atrial systole (peak A). The ratio of peak mitral flow velocity in early diastole to mitral flow velocity at the time of atrial systole was calculated (E/A ratio).

Statistics

The data were reported as the mean ± one standard deviation. The differences in H/M ratio, clearance, LVDed, LVDes, SF, peak E, peak A and E/A ratio were compared by a Student's t-test. A value < 0.05 was considered significant.

RESULTS

Case presentation

Myocardial ^{123}I-MIBG and ^{123}I-BMIPP anterior images of a patient treated with doxorubicin are shown in Figure 1. In ^{123}I-MIBG images, the left ventricular myocardium was not visible which indicated a marked decrease in cardiac ^{123}I-MIBG uptake. However, in ^{123}I-BMIPP images the myocardium was clearly visible, indicating a high left ventricular uptake of ^{123}I-BMIPP.

Scintigraphic results

The heart-to-mediastinum ratio (H/M ratio) was compared between the patients treated with anthracycline and the control subjects (Table 2). A H/M ratio of ^{123}I-MIBG was lower in patients treated with anthracycline than in control subjects (early: 1.5 ± 0.2 vs. 1.9 ± 0.2, $p < 0.01$, delay: 1.6 ± 0.3 vs. 2.0 ± 0.3, $p < 0.01$). The H/M ratio of ^{123}I-BMIPP was similar between the two groups (early: 2.1 ± 0.2 vs. 2.0 ± 0.2, delay: 1.9 ± 0.3 vs. 1.8 ± 0.2).

^{123}I-MIBG and ^{123}I-BMIPP clearance from the myocardium was compared between the anthracycline patients and the control subjects (Table 2). The clearance of ^{123}I-MIBG (27 ± 10% vs. 22 ± 4%, $p < 0.05$), but not ^{123}I-BMIPP (24 ± 6% vs. 26 ± 6%), was faster in patients treated with anthracycline than in the control subjects.

Table 2 Comparison of scintigraphic results

	Control (n = 10)	Anthracycline (n = 13)	p value
^{123}I -MIBG			
H/M ratio			
early	1.9 ± 0.2	1.5 ± 0.2	< 0.01
delay	2.0 ± 0.3	1.6 ± 0.3	< 0.01
clearance	22 ± 4%	27 ± 10%	< 0.05
^{123}I-BMIPP			
H/M ratio			
early	2.0 ± 0.2	2.1 ± 0.2	ns
delay	1.8 ± 0.2	1.9 ± 0.3	ns
clearance	26 ± 6%	24 ± 6%	ns

H/M ratio: heart-to-mediastinum ratio

When the H/M ratio of ^{123}I-MIBG smaller than mean – SD in the control subjects was considered abnormal, normal lower limits were 1.7 in both early and delayed ^{123}I-MIBG images. Similarly, normal upper limit for ^{123}I-MIBG clearance was determined as 26% from the values of control subjects (mean + SD). The sensitivities of ^{123}I-MIBG imaging for the detection of anthracycline cardiotoxicity were 77% (10 of 13 patients) by the H/M ratio in the early image, 69% (9 of 13) by the H/M ratio in the delayed image and 54% (7 of 13) by the clearance.

Table 3 Echocardiographic measurements

	Control	Anthracycline	p value
LVDed (cm)	4.8 ± 0.4	5.0 ± 0.9	ns
LVDes (cm)	3.0 ± 0.4	3.1 ± 0.6	ns
%SF (%)	36 ± 7	37 ± 8	ns
peak E (cm/sec)	66 ± 20	63 ± 22	ns
peak A (cm/sec)	43 ± 19	44 ± 24	ns
E/A	1.6 ± 0.3	1.4 ± 0.4	ns

LVDed: left ventricular dimension at end-diastole, LVDes: left ventricular dimension at end-systole, %SF: shortening fraction, peak E: peak mitral flow velocity in early diastole, peak A: peak mitral flow velocity in atrial systole, E/A: a ratio of peak E to peak A

Echocardiographic results

Echocardiographic measurements were compared between the patients treated with anthracycline and the control subjects (Table 3). The left ventricular end-diastolic dimension (LVDed), left ventricular end-systolic dimension (LVDes), left ventricular shortening fraction (%SF), mitral peak flow velocities at early diastole (peak E) and at atrial systole (peak A), and the ratio of peak E to peak A (E/A ratio) were comparable between the two groups.

DISCUSSION

The patients treated with anthracycline showed a lower uptake and faster clearance of ^{123}I-MIBG in the myocardium than the control subjects, although echocardiographic measurements were similar. Myocardial ^{123}I-BMIPP uptake and clearance were comparable between the two groups. The present findings suggest that myocardial imaging with ^{123}I-MIBG may be useful in detecting myocardial damage in patients treated with anthracycline at the early stage when cardiac systolic and diastolic function is still preserved.

Numerous methods have been used for the detection of anthracycline-induced cardiotoxicity. Among them, serial radionuclide angiography is an effective and practical way for monitoring anthracycline-induced cardiotoxicity.[9] However, the sensitivity of radionuclide-determined left ventricular ejection fraction (LVEF) at rest is relatively low, because local morphologic changes may precede a decrease in the LVEF. The contribution of exercise or pharmacologic stress testing remains still controversial, because an abnormal response in LVEF is nonspecific, and the stress test is often difficult to perform in patients with cancer.[6,8] Diastolic dysfunction precedes the impairment of systolic function in patients receiving doxorubicin treatment.[5] However, these changes in diastolic function are affected by several factors and are nonspecific.

Myocardial imaging with ^{99m}Tc-pyrophosphate[25] and ^{111}In-antimyosin[26] was used to detect doxorubicin cardiotoxicity. Carrio et al. have recently reported that intense antimyosin uptake was observed in all patients at intermediate cumulative doses.[27] Hiroe et al. have indicated in rats experiment that as the severity of morphological changes increases, there is an increase in myocardial antimyosin uptake.[28] They also show a strong correlation between the antimyosin uptake and left ventricular end-diastolic pressure.

Metabolic abnormality may precede functional changes, but in the present study ^{123}I-BMIPP was considered to be less useful in detecting anthracycline-induced myocardial damage. This is consistent with the experimental report that myocardial fatty acids uptake decreased only at high cumulative doses in adriamycin-induced cardiomyopathic rats.[21] Fatty acid utilization could not be changed, because cumulative doses of anthracycline were relatively low in the present study. Further evaluation is required before the value of ^{123}I-BMIPP imaging for the detection of anthracycline-induced myocardial damage can be accepted.

Recently, Wakasugi et al. have showed in a rat model of doxorubicin cardiomyopathy that ^{125}I-MIBG accumulation in the myocardium decreases in an adriamycin dose-dependent manner.[16,17] In the presence of normal LVEF and slight myocyte damage (scattered or focal vacuolar degeneration), ^{125}I-MIBG uptake is significantly reduced. They suggest that MIBG may be a sensitive biochemical marker of adriamycin cardiomyopathy. However, the application of this isotope has not been tested in clinical trials. In the present study, we showed that patients treated with anthracycline, who had normal cardiac systolic and diastolic function, showed a lower uptake and faster clearance of ^{123}I-MIBG in the myocardium than the control subjects.

Although tomographic images have advantages in assessing regional ^{123}I-MIBG and ^{123}I-BMIPP uptake, we used the anterior projection images. In 3 patients in whom the H/M ratio of ^{123}I-MIBG was less than 1.3, tomographic images could not be reconstructed, because the count density was insufficient for image reconstruction. The heart-to-mediastinum ratio (H/M ratio) obtained from the anterior image was used to quantify cardiac ^{123}I-MIBG uptake in the present study. It was reported that the H/M ratio of ^{123}I-MIBG uptake was significantly related to the myocardial norepinephrine concentration[22] and most potent to predict survival in patients with heart failure.[23]

Mechanisms for the decreased uptake and faster clearance of ^{123}I-MIBG in anthracycline-induced cardiomyopathy are still disputed. The following two mechanisms are the most relevant. The first is the disturbance of MIBG retention in the intraneural norepinephrine storage vesicles in patients treated with anthracycline.[29,30] It was reported that the larger proportion of extra-vesicular ^{123}I-MIBG in patients with dilated cardiomyopathy might account for more rapid washout of ^{123}I-MIBG, because MIBG was more firmly bound inside norepinephrine storage vesicles than outside.[29] The second is enhanced exocytotic release and turnover of MIBG due to systemic

adrenergic hyperactivity. There is an increase in plasma norepinephrine and a decrease in myocardial norepinephrine, reflecting systemic hyperactivity of the adrenergic nervous system, in adriamycin-induced cardiomyopathic rats.[16]

Carrio et al.[27] have recently reported that patients with sarcomas treated with continuous infusion of adriamycin present with less antimyosin uptake than those treated with a bolus injection, thus indicating less severe cardiotoxicity. Early detection of patients at risk for cardiotoxicity before cardiac function deteriorates has important clinical implications, since drug administration schedules can be individually changed to reduce the incidence and severity of heart failure.[31] Our results indicated that myocardial imaging with ^{123}I-MIBG might detect patients at risk for anthracycline cardiotoxicity at an early stage when cardiac function was still preserved.

REFERENCES

1. Lefrak EA, Pitha J, Rosenheim S, Gottleib JA. A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer* 32: 302–314, 1973.
2. Henderson IC, Frei III. Adriamycin and the heart. *N Engl J Med* 300: 310–312, 1979.
3. Fu LX, Waagstein F, Hjalmarson A. A new insight into adriamycin-induced cardiotoxicity. *Int J Cardiol* 29: 15–20, 1990.
4. Von Hoff DD, Rozencweig M, Piccart M. The cardiotoxicity of anticancer agents. *Semin Oncol* 9: 23–33, 1982.
5. Marchandise B, Schroeder E, Bosly A, Doyen C, Weynants P, Kremer R, et al. Early detection of doxorubicin cardiotoxicity: Interest of Doppler echocardiographic analysis of left ventricular filling dynamics. *Am Heart J* 118: 92–98, 1989.
6. Klewer SE, Goldberg SJ, Donnerstein RL, Donnerstein RL, Berg RA, Hutter JJ. Dobutamine stress echocardiography: A sensitive indicator of diminished myocardial function in asymptomatic doxorubicin-treated long-term survivors of childhood cancer. *J Am Coll Cardiol* 19: 394–401, 1992.
7. Alexander J, Dainiak N, Berger HJ, Goldman L, Johnstone D, Reduto L, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiography. *N Engl J Med* 300: 278–283, 1979.
8. Palmeri ST, Bonow RO, Myers CE, Seipp C, Jenkins J, Green MV, et al. Prospective evaluation of doxorubicin cardiotoxicity in rest and exercise radionuclide angiography. *Am J Cardiol* 58: 607–613, 1986.
9. Schwartz RG, Mckenzie WB, Alexander J, Sager P, D'souza A, Manatunga A, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. *Am J Med* 82: 1109–1118, 1987.
10. Olmos RAV, Huinink WWB, Greve JC, Hoefnagel CA. I-123 MIBG and serial radionuclide angiocardiography in doxorubicin-related cardiotoxicity. *Clin Nucl Med* 17: 163–167, 1992.
11. Isner JM, Ferrans VJ, Cohen SR, Witkind BG, Virmani R, Gottdiener JS, et al. Clinical and morphologic cardiac findings after anthracycline chemotherapy. Analysis of 64 patients studied at necropsy. *Am J Cardiol* 51: 1167–1174, 1983.
12. Druck MN, Gulenchyn KY, Evans WK, Gotlieb A, Srigley JR, BarShlomo B, et al. Radionuclide angiography and endomyocardial biopsy in the assessment of doxorubicin cardiotoxicity. *Cancer* 53: 1667–1674, 1984.
13. Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu J, Clinthorne NH, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 22: 22–31, 1981.
14. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jacques S. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 28: 1620–1624, 1987.
15. Dae MW, O'Connell JW, Botvinick EH, Ahearn T, Yee E, Huberty JP, et al. Scintigraphic assessment of regional cardiac adrenergic innervation. *Circulation* 79: 634–644, 1989.
16. Wakasugi S, Wada A, Hasegawa Y, Nakano S, Shibata N. Detection of abnormal cardiac adrenergic neuron activity in adriamycin-induced cardiomyopathy with iodine-125-metaiodobenzylguanidine. *J Nucl Med* 33: 208–214, 1992.
17. Wakasugi S, Fischman AJ, Babich JW, Aretz T, Callahan RJ, Nakaki M, et al. Metaiodobenzylguanidine: Evaluation of its potential as a tracer for monitoring doxorubicin cardiomyopathy. *J Nucl Med* 34: 1282–1286, 1993.
18. Knapp FF, Ambrose KR, Goodman MM. New radioiodinated methylbranched fatty acids for cardiac imaging. *Eur J Nucl Med* 12: S39–S44, 1986.
19. Takeishi Y, Chiba J, Abe S, Tonooka I, Komatani A, Tomoike H. Heterogeneous myocardial distribution of iodine-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) in patients with hypertrophic cardiomyopathy. *Eur J Nucl Med* 19: 775–782, 1992.
20. Randle PJ, Tubbs PK. Carbohydrate and fatty acids metabolism. *In* Handbook of physiology, Berne RM (ed.). Bethesda. American Physiological Society.
21. Wakasugi S, Fischman AJ, Babich JW, Callahan RJ, Elmaleh DR, Wilkinson R, et al. Myocardial substrate utilization and left ventricular function in adriamycin cardiomyopathy. *J Nucl Med* 34: 1529–1535, 1993.
22. Schofer J, Spielmann R, Schuchert A, Weber K, Schluter M. Iodine-123 meta-iodobenzylguanidine scintigraphy: A non-invasive method to demonstrate myocardial adrenergic nervous system disintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 12: 1252–1258, 1988.
23. Merlet P, Valette H, Dubois-Rande JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med* 33: 471–477, 1992.
24. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantification in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 56: 457–462, 1977.
25. Miyagawa M, Tanada S, Hamamoto K. Scintigraphic evaluation of myocardial uptake of thallium 201 and technetium 99m pyrophosphate utilizing a rat model of chronic doxorubicin cardiotoxicity. *Eur J Nucl Med* 18: 332–338, 1991.

26. Estorch M, Carrio I, Berna L, Martinez-Duncker C, Alonso C, Germa JR, et al. Indium-111-antimyosin scintigraphy after doxorubicin therapy in patients with advanced breast cancer. *J Nucl Med* 31: 1965–1969, 1990.
27. Carrio I, Lopez-Pousa A, Estorch M, Duncker D, Berna L, Torres G, et al. Detection of doxorubicin cardiotoxicity in patients with sarcomas by indium-111-antimyosin monoclonal antibody studies. *J Nucl Med* 34: 1503–1507, 1993.
28. Hiroe M, Ohta Y, Fujita N, Nagata M, Toyozaki T, Kusakabe K, et al. Myocardial uptake of ^{111}In monoclonal antimyosin Fab in detecting doxorubicin cardiotoxicity in rats. Morphological and hemodynamic findings. *Circulation* 86: 1965–1972, 1992.
29. Henderson EB, Kahn JK, Corbett JR, Jansen DE, Pippin JJ, Kulkarni P, et al. Abnormal I-123 metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive cardiomyopathy. *Circulation* 78: 1192–1199, 1988.
30. Rabinovitch MA, Rose CP, Schwab AJ, Fitchett DH, Honos GN, Stewart JA, et al. A method of dynamic analysis of iodine-123-metaiodobenzylguanidine scintigrams in cardiac mechanical overload hypertrophy and failure. *J Nucl Med* 34: 589–600, 1993.
31. Legha SS, Benjamin RS, Mackay B, Ewer M, Wallace S, Valdivieso M, et al. Reduction of doxorubicin cardiotoxicity by a prolonged continuous intravenous infusion. *Ann Int Med* 96: 133–139, 1982.