EDITORIAL

Antimyosin Cardiac Imaging: Will It Play a Role in the Detection of Doxorubicin Cardiotoxicity?

Doxorubicin (Adriamycin), an anthracycline glycoside antibiotic, is a potent chemotherapeutic agent useful in the treatment of a wide variety of tumors (*1–3*). Cardiotoxicity, the most serious adverse effect, is a well recognized clinical entity, which may limit its use (*4,5*). This is characterized in extreme cases by progressive left ventricular dysfunction and heart failure which may be fatal. The cardiotoxicity is believed to be mediated by free radicals, produced by the metabolites of doxorubicin. Generally, the left ventricular dysfunction is irreversible, although in a small percentage of cases there may be spontaneous improvement in left ventricular function following the discontinuation of chemotherapy (*6*).

The incidence and severity of doxorubicin cardiotoxicity increases with cumulative doses; however, there is considerable variation in the individual susceptibility to cardiotoxic effects (*4,7*). Some individuals may develop severe cardiac dysfunction and even fatal congestive heart failure at relatively lower doses, whereas others may tolerate considerably larger doses with only minimal cardiac effects. In general, additional treatment after reaching a cumulative dose of 500 mg/m^2 produces a significantly increasing incidence of clinically relevant cardiomyopathy. The incidence of congestive heart failure is under 2% at total cumulative dose of 400 mg/m^2 or less, 7% at 550 mg/m^2, and may rise to greater than 20% at cumulative doses in excess of 700 mg/m^2 (*8*). Due to differences in the susceptibility to the cardiotoxic effects of doxorubicin, it is difficult to fix arbitrarily a ceiling for the cumulative dose limit of doxorubicin. At a lower dose limit, there will be fewer cases with serious cardiotoxicity. However, this strategy would deny treatment with a potent and effective agent to many who would tolerate much higher doses and potentially benefit from its highly relevant antineoplastic therapeutic effects.

The current strategy is to administer doxorubicin up to a point beyond which further therapy would result in cardiotoxicity, requiring an ability to monitor for cardiotoxicity and safely titrate the cumulative dose of doxorubicin accordingly (*9,10*). A significant reduction in the incidence of severe doxorubicin cardiotoxicity has been achieved with the use of this approach. Elderly patients, patients with preexisting cardiac disease, hepatic dysfunction, and those with prior mediastinal irradiation are more prone to develop doxorubicin cardiotoxicity; but there are no specific markers to predict individual predisposition to doxorubicin cardiotoxicity. Although, a number of noninvasive and invasive tests to monitor the cardiotoxicity of doxorubicin have been used in the past, only radionuclide angiocardiography and endomyocardial biopsy have proven clinically useful (*11–14*).

On endomyocardial biopsy, the histologic changes of doxorubicin cardiotoxicity consist in order of increasing severity, of swelling of sarcoplasmic reticulum, cytoplasmic vacuolization, myofibrillar degeneration, myocyte disruption, and fibrosis. These changes are seen most clearly on electron microscopy; while the changes noted on conventional microscopy are less specific. The severity of these structural changes is taken into consideration when monitoring cardiotoxicity and choosing the dose limit. Higher grades of change are associated with or considered to be predictive of impending congestive heart failure.

On the other hand, radionuclide angiocardiography at rest monitors an important physiologic index of cardiac function. Overt congestive heart failure is preceded by a progressive fall in left ventricular ejection fraction (LVEF). Serial studies can detect a change in cardiac function over time and doxorubicin administration can be stopped when a predetermined fall in LVEF is observed. Both the level of final LVEF and the magnitude of the fall are important determinants (*10*). Schwartz et al. have described guidelines for utilizing serial radionuclide angiocardiography at rest during the course of doxorubicin therapy, based upon an experience with just under 1,500 patients over a 7-yr period (*10,14*). Table 1 describes these guidelines. Over four-fold reduction in the incidence of overt cardiac failure was observed where these guidelines were followed. Moreover, if congestive heart failure did develop, it was mild and

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TABLE 1
Guidelines for Monitoring Doxorubicin Cardiotoxicity by Serial Radionuclide Angiocardiography*

Baseline evaluation: Baseline radionuclide angiocardiography (RNA) at rest to estimate LVEF prior to the commencement of doxorubicin therapy or before 100 mg/m^2 of doxorubicin has been given.

Subsequent evaluations: Subsequent studies are performed 3 wk after the indicated last dose of doxorubicin and prior to the consideration of next dose at the following intervals:

I. Patients with normal baseline LVEF (≥50%)
   A. Second study after 250–300 mg/m^2.
   B. Repeat study after 400 mg/m^2 in patients with known heart disease, hypertension, radiation exposure, abnormal EKG, or cyclophosphemide therapy; or after 450 mg/m^2 in the absence of above risk factors.
   C. Obtain sequential studies thereafter prior to each dose.

Discontinue doxorubicin therapy once functional criteria for cardiotoxicity develop, i.e., absolute decrease in LVEF ≥10% (EF Units) to a level <50% (EF Units).

II. Patients with abnormal baseline LVEF (<50%)
   A. *With baseline LVEF <30%, doxorubicin should not be started.*
   B. With baseline LVEF >30% and <50%, perform study prior to each dose.

Discontinue doxorubicin with absolute decrease in LVEF ≥10% (EF Units) and/or final LVEF ≤30%.

* Modified from Ref. 14.

responsive to routine medical therapy. The same beneficial results were obtained whether these guidelines were used in the setting of a community or university hospital (*14*).

Whereas endomyocardial biopsy is an invasive and expensive technique that requires a skilled histopathologist for the interpretation of the specimen, radionuclide angiocardiography at rest is a noninvasive and easy to perform technique, which can be performed repeatedly. In a retrospective necropsy study of 64 patients treated with anthracyclines, 48% of patients showed variable degree of histologic changes in the absence of any clinical evidence of cardiotoxicity (*15*). In the same study, it was also observed that 35% of patients who showed evidence of anthracycline cardiotoxicity during life showed no specific histologic changes on light microscopy. Though based on light microscopy, these observations indicate the potential limitations of relying on histologic changes for predicting significant anthracycline cardiotoxicity. Moreover, the studies comparing the two techniques have shown that histologic abnormalities may be observed even after relatively small cumulative doses of doxorubicin, with no evidence of functional impairment.

Although higher grades of changes are associated with a higher frequency and greater severity of left ventricular dysfunction, a linear correlation between the grade of histopathologic change and deterioration in left ventricular function is frequently not seen. It seems that structural changes on biopsy appear much before any clinically relevant functional deterioration. Physiologic reserve and normal compensatory responses are able to maintain normal myocardial function until a certain threshold is crossed (*13*). Over 50% of asymptomatic patients show evidence of some cardiac damage on endomyocardial biopsy after they have received a cumulative dose of 550 mg/m^2 of doxorubicin.

It has also been observed that some patients with normal resting LVEF on radionuclide angiocardiography show an abnormal response to exercise (*16*), but this is a nonspecific sign and a significant proportion of patients with malignancies cannot undergo exercise testing because of generalized debility or musculoskeletal problems. The value of this finding in guiding doxorubicin therapy is limited. To date, serial resting radionuclide angiocardiography appears the most practical and effective way of monitoring doxorubicin cardiotoxicity.

Recently, the immunoscintigraphic agent indium-111- (^{111}In) labeled antimyosin antibody (Fab), developed originally for the imaging of myocardial necrosis in patients with acute myocardial infarction, has been employed for the evaluation of conditions characterized by diffuse myocardial cell injury such as myocarditis, cardiomyopathy, and cardiac transplant rejection. This agent localizes specifically in myocardial cells with acute irreversible damage to the myocyte membrane (*17*). Initial studies with this agent indicate promise in the evaluation of patients with myocarditis and cardiac transplant rejection (*18–20*). The paper by Estorch et al. in this issue of *The Journal of Nuclear Medicine* is a first attempt to use ^{111}In-antimyosin in the evaluation of doxorubicin cardiotoxicity in man (*21*). They performed ^{111}In-antimyosin imaging in 20 patients with breast carcinoma after they had received a cumulative dose of 500 mg/m^2 of doxorubicin in combination chemo-

therapy. Abnormal myocardial localization of the radiotracer was noticed in 17 (85%) patients. They also performed radionuclide angiocardiography before starting therapy and after patients had received a cumulative dose of 500 mg/m^2 of doxorubicin. A ≥10% fall in LVEF was observed in four (20%) patients. Based upon these findings, it was concluded that antimyosin scintigraphy is a highly sensitive technique for the detection of doxorubicin cardiotoxicity.

Though the concept of exploring ^{111}In-antimyosin imaging to detect doxorubicin cardiotoxicity at an earlier and preventable stage is of interest, several important issues have not as yet been addressed. Only a small number of patients have been studied. Whether these observations are applicable to larger and more diverse patient populations is not clear. Moreover, Estorch et al. did not monitor cardiac function until patients received a total of 500 mg/m^2 of doxorubicin, which is distinct from currently proposed guidelines (*14*). Two out of 20 patients had evidence of left ventricular dysfunction prior to the commencement of doxorubicin therapy as evidenced by a LVEF of <50%. They should have had left ventricular function monitored even more closely (*9,14*). This unmonitored fixed-dose regimen of doxorubicin is unsafe and should not be used in clinical practice. A new technique for detection of doxorubicin cardiotoxicity should be compared with the existing guidelines for detection and prevention (Table 1). With more frequent monitoring, many of their patients might have had doxorubicin therapy discontinued at relatively lower doses; whereas the patients who showed no change in LVEF after receiving 500 mg/m^2 of doxorubicin might have been allowed to receive further doses of the drug, if indicated clinically. The authors have not used any standard criteria for diagnosing doxorubicin cardiotoxicity in their study. A change of <5% in LVEF as an end point is too nonspecific for diagnosing doxorubicin cardiotoxicity. Using standard criteria, which should include both the fall in LVEF and the level achieved, only 4 of 20 (20%) patients could be considered to have cardiotoxicity. The finding of abnormal ^{111}In-antimyosin uptake in 17/20 (85%) patients, thus, indicates a lack of specificity in the detection of doxorubicin cardiotoxicity.

Indium-111-antimyosin imaging can find a role in monitoring and prevention of doxorubicin cardiotoxicity if it can fulfill at least some of the following requirements:

1. Patients showing evidence of significant left ventricular dysfunction at any dose of doxorubicin show positive tracer localization.
2. Patients showing no abnormal ^{111}In-antimyosin uptake do not show any evidence of left ventricular dysfunction and can receive further doses of doxorubicin without risk of serious cardiotoxicity.
3. The intensity of abnormal tracer uptake correlates in some manner with the severity of left ventricular dysfunction.
4. Abnormal tracer uptake precedes the development of significant left ventricular dysfunction in the presence of continued doxorubicin therapy. This finding would alert the treating physician to the possibility of impending doxorubicin cardiotoxicity at a stage when left ventricular function has not changed. This also may allow modification of the regimen of doxorubicin administration, depending upon the clinical picture of the patient.
5. In patients who show evidence of cardiotoxicity, this study provides some information about the reversibility of the condition.
6. The test must be suitable for serial study in order to guide the course of therapy.

Currently, there is insufficient data to indicate whether ^{111}In-antimyosin imaging can be used as a primary test for guiding doxorubicin therapy. It seems more likely that it can complement the information derived from radionuclide angiocardiography. By combining the two techniques, it may be possible to gain greater insight into the process of doxorubicin cardiotoxicity.

There are several other issues which also have not as yet been addressed. What is the optimal timing for performing ^{111}In-antimyosin imaging during the course of doxorubicin therapy and how frequently should it be performed? Is there any relationship between the results of ^{111}In-antimyosin imaging and the structural changes observed on endomyocardial biopsy? It is well known that structural changes precede the deterioration in left ventricular function. A very high proportion (85%) of abnormal ^{111}In-antimyosin localization after treatment with 500 mg/m^2 of doxorubicin suggests some similarity. Do findings on ^{111}In-antimyosin imaging correlate better with structural changes rather than with the functional abnormalities? A comparison between the intensity of abnormal radiotracer uptake and both the severity of structural changes and left ventricular dysfunction also is required. What are the prognostic implications of abnormal ^{111}In-antimyosin uptake on the initial imaging? Does a change in this finding on follow-up study indicate a reversal? In a recent study

of ^{111}In-antimyosin imaging in patients with unexplained congestive heart failure and suspected myocarditis, Dec et al. observed a favorable prognosis in those with abnormal ^{111}In-antimyosin uptake, irrespective of the histopathologic biopsy findings (*18*). In that patient cohort, it appears that positive images are indicative of active myocyte necrosis whereas negative images indicate myocardial fibrosis with very little chance of improvement. Will the same be true of doxorubicin cardiotoxicity? In the same study, the authors also observed persistent positivity of ^{111}In-antimyosin images when repeated several months later despite an improvement in left ventricular function in some cases. It is worth exploring whether ^{111}In-antimyosin imaging in patients who have received intermediate doses of doxorubicin (250–350 mg/m^2) can effectively classify patients. On the other hand, persistent positivity of images may present a problem. The safe therapeutic windows for further doxorubicin in patients with negative ^{111}In-antimyosin images, as well as that for patients with positive images but unaltered cardiac function, require definition. This information is necessary before ^{111}In-antimyosin imaging can be established as a primary or adjunctive modality for the evaluation of doxorubicin cardiotoxicity.

The present paper in this *Journal* certainly stimulates interest and points out potential. However, definite conclusions cannot as yet be made. At present, we would suggest that evaluation of resting left ventricular function still remain the noninvasive modality of choice for assessing doxorubicin cardiotoxicity. Large, well-planned prospective studies are required to resolve the relevant issues raised by the Estorch et al. paper and this editorial. Only with a large data base exploring interactive aspects of left ventricular function and ^{111}In-antimyosin imaging can algorithms based upon ^{111}In-antimyosin imaging be developed. Such algorithms may also provide a useful means of evaluating alternative therapeutic strategies designed to obviate cardiotoxicity, such as the alternative methods of drug administration (*8,22,23*), co-administration of agents expected to be cardioprotective (*24*), or the use of newer analogues of doxorubicin (*25,26*).

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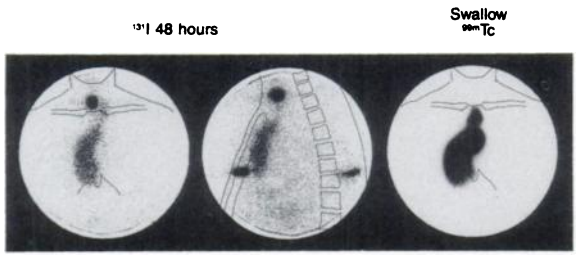

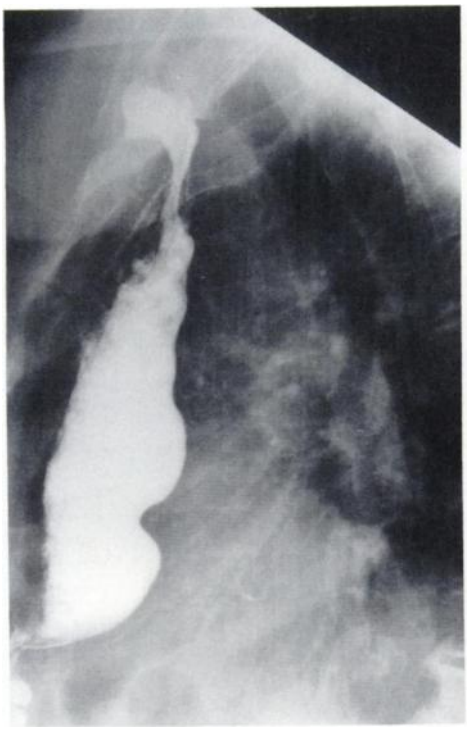

FIRST IMPRESSIONS

PURPOSE:
A 62-yr-old man with papillary cancer of the thyroid, who underwent a left total and right subtotal lobectomy at another institution six weeks prior to this examination, was referred for ablative thyroid therapy. A neck and chest scan at 48 hr with ^{131}I demonstrated activity over the thyroid bed (4.0%) and in the right mediastinum (7.3%). A large intrathoracic mass raised the question of intrathoracic stomach or mediastinal metastasis. To further define the anatomy, $^{99m}TcO_4$ was administered orally. Immediate images revealed activity in the exact distribution of the ^{131}I uptake. Previously, an examination confirmed the presence of a short esophagus with an intrathoracic stomach. The patient had undergone a cervical esophagogastrostomy for achalasia several years earlier. Subsequent esophagogastroduodenoscopy substantiated the presence of 2–3 cm of remaining esophagus with the entire stomach residing in the thorax. The ^{131}I scan was thus interpreted as showing remnant thyroid tissue just above the sternal notch. Iodine-131 acivity to the left of it and in the mediastinum was in the short esophagus and stomach.

TRACER:
3 mCi ^{131}I and 0.5 mCi $^{99m}TcO_4$

ROUTE OF ADMINISTRATION:
Oral

TIME AFTER INJECTION:
^{131}I: 48 hr
$^{99m}TcO_4$: Immediate

INSTRUMENTATION:
Siemens dual-head whole-body scanner
GE 500 large field of view camera

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