individual management of patients with previous risk factors or for patients who are potential candidates for future repeated doxorubicin administration. Although the prognosis for patients with advanced or metastatic soft-tissue sarcomas is still poor, this may be particularly relevant in young patients with responsive tumors who might benefit from further doxorubicin administration. Recently, it has been shown in children treated with doxorubicin for acute lymphoblastic leukemia that decreased contractility may occur several years after chemotherapy (*21*). An unexpectedly high incidence of late cardiac abnormalities in these children was reported in that study. It is possible that early detection of cardiotoxicity in these circumstances could prompt changes in the schedule of administration which could result in decreased cardiotoxicity over time.

We conclude that antimyosin studies are helpful in the assessment of doxorubicin cardiotoxicity. Intense antimyosin uptake (HLR ≥ 1.90) at intermediate cumulative doses identifies patients at risk of cardiotoxicity before LVEF deteriorates. Antimyosin studies provide a new quantitative method to compare different administration regimens. Patients with sarcomas treated by continuous infusion present with less antimyosin uptake than those treated with bolus injection, thus indicating less severe cardiotoxicity.

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EDITORIAL

Antimyosin Positivity in Doxorubicin Cardiotoxicity: Earlier Than the Conventional Evidence

The classical symptom of chest pain almost invariably offers an indication of acute myocardial infarction. Electrocardiographic changes and enzyme elevation are the tell-tale accompaniments. However, the classical symptoms and diagnostic methods are not foolproof. The need for an accurate diagnostic method for the detection of ischemic necrosis led to development of antimyosin scintigraphy. The imaging procedure demonstrated high diagnostic accuracy for the detection of an acute myocardial infarction (*1–7*). The high predictive values of normal and abnormal scans confirmed the clinical utility of the procedure in patients with equivocal diagnosis resulting from inadequate or uninterpretable clinical or electrocardiographic alterations (*8*). These studies established the lack of sarcolem-

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mal integrity (represented by antibody entry into the cell) as an indicator of irreversible myocardial injury (*9–13*).

Since diffuse myocyte necrosis forms the common pathological substrate in primary or secondary myocarditis and cardiac transplant rejection, it was reasoned that antimyosin scintigraphy may be of value in the recognition of the active stage of these disorders regardless of etiology. Studies have revealed that antimyosin scintigraphy detected almost all cases of myocarditis (*14–16*) and cardiac transplant rejection (*17–19*) where there was biopsy evidence of myocyte necrosis (high sensitivity). Patients with negative antimyosin scans were confirmed by endomyocardial biopsies (high negative predictive value). Antimyosin imaging may be a useful screening tool prior to undertaking an invasive biopsy procedure (*15,18*), since a negative scan reliably correlates with absence of disease. However, there exists a large proportion of positive scans where there was no corresponding biopsy-evidence of myocyte necrosis resulting in low specificity and low positive predictive values (*15,19*). Whether these are false-positive scans or the biopsy missed lesions due to sampling error (false-negative biopsy) needed to be resolved.

Dec et al. performed antimyosin scans in patients with acute onset of congestive heart failure (CHF) for possible noninvasive detection of myocarditis (*15*). In a subgroup of 48 patients, 26 had a positive scan but only 10 had positive biopsy for myocarditis. The clinical course of these scan-positive patients was comparable regardless of their biopsy results. Both concordant-scan and discordant-scan positive patients had a higher likelihood of substantial improvement in left ventricular ejection fraction, than 22 patients who had negative antimyosin scans. Since improvement in the left ventricular systolic function is a recognized feature of myocarditis, a subset of patients with discordant positive scans may have had myocarditis which right ventricular biopsy had failed to detect. False-negative biopsy rather than a false-positive scan, however, does not appear to be a complete explanation of the discrepancy.

Ballester et al. have performed serial antimyosin scans in cardiac transplant recipients and correlated them with simultaneously performed right ventricular endomyocardial biopsies (*19*). Although a large number of positive scans were not corroborated by histologically verified moderate graft rejection, there was a high likelihood of subsequent yield of a positive biopsy in patients with discordant-positive antimyosin scans. On the other hand, patients with negative scans had the least likelihood of subsequent biopsies with evidence of rejection. Furthermore, a large proportion of patients with positive scans did demonstrate mild histopathologic graft rejection (mononuclear cell infiltration but no myocyte necrosis). This study offered an indirect explanation of an earlier identification of onset of myocyte necrosis by antimyosin imaging relative to biopsy evidence. It is reasonable to conceive that an antibody should be able to recognize tiny sarcolemmal breaches before disintegration of sarcolemmal continuity manifests itself as histologically definable myocyte necrosis.

Empirical demonstration of the correlation between antimyosin positivity and sarcolemmal disruption was performed using 1-μ diameter polystyrene beads coated with antimyosin antibody (*9*). These cells which allow access to 1-μ beads are therefore frankly necrotic. On the other hand, clinical trials use Fab fragments of antimyosin antibody. Fab has a substantially smaller dimension (35 × 65 Å) than the antimyosin coated beads (*20*). Theoretically, Fab fragments should be able to enter membrane gaps as small as those created by compliment membrane attack complexes (diameter, 100 Å) or those created by cytotoxic lymphocytes (diameter, 160 Å) (*21*). Such small sarcolemmal breaches are only visualized by high-resolution electronmicroscopy. With ensuing intracellular edema and extrusion of intracellular contents with time, identification by light microscopy subsequently becomes possible. Small cell membrane breaches, undetectable by histology, nevertheless should enable intracellular access to Fab. Therefore, antimyosin uptake should represent early evidence of cardiac myocyte necrosis.

The study by Carrio et al. published in this issue of the *Journal* corroborated the concept that antimyosin uptake (*22*) preceded appearance of other criteria of myocardial injury such as systolic dysfunction, the current gold standard for guidance of doxorubicin therapy (*23*). Significant antimyosin uptake was observed at intermediate cumulative doxorubicin doses when left ventricular systolic function was still maintained (*22*). This appears logical, since significant myocardial damage would have to occur before functional impairment can be detected. The investigators demonstrated a direct correlation between the dose of doxorubicin and the magnitude of myocyte damage as reflected by antimyosin uptake. They demonstrated that patients with greater myocardial antimyosin antibody uptake had higher likelihood of developing congestive failure at maximal doxorubicin dosage. Furthermore, the patients who were treated with continuous doxorubicin infusion had less antimyosin uptake than those treated with a bolus of doxorubicin at all levels of cumulative doses. Simultaneous assessment of left ventricular function in these two groups supported severe myocardial injury in the bolus group. Although the investigators demonstrated the occurrence of cardiotoxicity by antimyosin scintigraphy, nevertheless, two important issues remain to be resolved.

Pathologic Basis for the Antimyosin Positivity in Doxorubicin Toxicity

The histopathological abnormalities of doxorubicin cardiotoxicity as demonstrated by endomyocardial biopsy consist of swelling of sarcoplasmic reticulum, cytoplasmic vacuolization, myofibrillar degeneration, myocyte disruption and fibrosis (*24*). Higher grades of changes are predictive of im-

pending CHF. Since myofibrillarlysis or vacuolization is the most common pathological finding, it is difficult to understand how this abnormality would be antimyosin-positive. Several investigators view the myofibrillarlytic cells as irreversibly damaged and the antimyosin uptake by these cells can be explained (*25,26*). On the other hand, other investigators suggest that these cells may still be viable because intracellular enzymes are preserved (*27*). It is possible that myofibrillarlysis may comprise a spectrum of mild damage to frankly necrotic myocytes. Positive antimyosin may be a marker of a subset of myocytes with a loss of sarcolemmal integrity that may or may not be histologically apparent. Prospective ultrastructural studies are needed to correlate positive antimyosin with the status of the sarcolemma. Immunoelectron microscopic studies in the biopsies performed immediately after the antimyosin scintigraphy may be of immense value.

Clinical Significance of Antimyosin Positivity in Patients Treated with Doxorubicin

Almost all patients in the present study, even at intermediate doses, demonstrated antimyosin uptake that cannot form a cut-off point for withdrawal of therapy. What would be the utility of a new test if therapy is to be continued in spite of the demonstration of myocyte damage by the test? If there were a group of patients that had not shown antimyosin uptake at high doses and if that allowed continuation of a supernormal dosage schedule, the contribution of antimyosin technology would have been paramount. At present, the only apparent contribution of this technology is the selection of an anti-neoplastic agent with a lower risk of cardiotoxicity, or demonstration of the validity of an agent that can prevent doxorubicin toxicity (such as antioxidants) or doxorubicin administration schedules that affect the myocardium less adversely.

Although skepticism may exist regarding the clinical use of antimyosin scintigraphy in doxorubicin cardiotoxicity, the present article has offered major insights into the pathophysiological characteristics of myocyte necrosis. It has also reconfirmed the feasibility of antibody-based detection of diffuse myocyte necrosis.

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