^{111}In Antimyosin Monoclonal Antibody in the Detection of Doxorubicin Cardiotoxicity: a Comparison with Histology and ^{99m}Tc Pyrophosphate†

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= Abstract = **Recently, ^{111}In-antimyosin monoclonal antibidies (^{111}In-AMAb) have been introduced for the diagnosis of myocardial infarction. The purpose of this study was to investigate the feasibility of using this agent for the early detection of cardiac damage induced by doxorubicin. The degree of drug induced change in the myocardium was evaluated histologically. ^{99m}Tc pyrophosphate (^{99m}Tc-PYP), known to preferentially accumulate in Adriamycin caused lesions, was used as a control radiopharmaceutical. Myocardial uptake of ^{111}In-AMAb and ^{99m}Tc-PYP was measured in 12 controls and 10 Adriamycin treated rabbits. The results indicated the following: 1) ^{111}In-AMAb uptake in the heart correlated well with the degree of pathology (r=0.95); 2) ^{99m}Tc-PYP uptake was also correlated with cardiac damage (r=0.77); 3) The uptake ratio (expressed as percent injected dose per gram myocardial tissue) of Adriamycin treated animals vs. controls was 2.7:1 for ^{111}In-AMAb and 9.2 for 99mTc-PYP nt 24 and 2 hours after intravenous injection, respectively; 4) considerable non-specific ^{99m}Tc-PYP accumulation was measured in the lungs and kidneys and was significantly higher in drug treated animals compared to controls. ^{111}In-AMAb accumulation remained unchanged in these organs. We conclude that ^{111}In-AMAb accurately detects cardiac toxicity induced by Adriamycin but that ^{99m}Tc-PYP still remains an acceptable agent in part because, of its availability and higher tracer concentration in the cardiac lesions.**

Key Words: *^{111}In-antimyosin monoclonal antibody, Adriamycin cardiac toxicity, ^{99m}Tc-pyrophosphate*

INTRODUCTION

Adriamycin (Doxorubicin hydrochloride), an anthracycline antibiotic, is a highly effective and commonly used chemotherapeutic agent. However, it can cause a severe and fatal form of

delayed irreversible cardiotoxicity. There is no reliable method to predict clinically significant cardiac toxicity and the pathogenic mechanism of Adriamycin induced cardiomyopathy has not been elucidated. Some investigators have utilized left ventricular ejection fraction to determine cardiotoxicity but the method is insensitive because myocardial damage must already be extensively present to depress global function for definite detection.

Infarct-avid radiopharmaceuticals such as ^{99m}Tc-pyrophosphate (PYP) and a newly developed agent, radiolabeled antimyosin antibody (AMAb) have been shown to be useful for the detection of myocardial injury and are used commonly in the diagnosis of acute myocardial infarction (Khaw et al. 1976; Khaw et al. 1978; Parkley et al. 1974; Botvinick et al. 1975; Khaw et al. 1980; Beller et al. 1977;Lee et al. 1991).

The purpose of this investigation was to determine the accumulation of ^{111}In-antimyosin monoclonal antibody in rabbit myocardium with experimentally induced cardiac damage caused by the intravenous administration of Adriamycin at doses previously felt to be subtoxic and to compare these results with those of ^{99m}Tc-pyrophosphate accumulation and histologic findings in the same animal.

MATERIALS AND METHODS

The monoclonal antimyosin antibody used in this study was a Fab fragment of IgG derived from BALB/c mice (R11D10), having specific affinity to human cardiac myosin. Two mCi of ^{111}In-Cl$_3$ were added to an aliquot of 0.5mg of DTPA-R11D10 Fab in 0.1 M citrate buffer (pH 5.0). The reaction mixture was gently mixed at room temperature for 10 minutes. Before administration the labeled antibody was filtered through 0.22 um micropore protein binding filter (Gelem). The average ^{111}In binding efficiency, measured by Sephadex column chromatography was 90%.

This study was performed in twenty-two mature New Zealand White rabbits weighing between 8 to 10 pounds. Ten drug treated and 12 control rabbits were used. The treated group of animals received 2.5 mg/kg Adriamycin by intravenous injection once each week for 4 weeks via the marginal ear vein while the control group received the same volume of 0.9% saline solution. Adriamycin was freshly prepared before each injection.

All animals were injected with 40-50 uCi of ^{111}In-antimyosin antibody at 24 hours before scheduled sacrifice and 200-250 μCi of ^{99m}Tc-pyrophosphate at 2 hours before sacrifice. At the end of the experiment, the rabbits were sacrificed by intravenous injection of 120mg of pentobarbitol. The heart was divided into left ventricle, right ventricle, septum and atrial portions and multiple transmural myocardial specimens were obtained. Weighed sections of each organ were counted in a well scintillation counter along with appropriate standards. The percentage of injected dose/gm tissue was calculated. Slices of myocardium and kidney were fixed in buffered neutral formalin, embedded in paraffin, and tissue sections were stained with Masson's trichrome and hematoxyline-eosin. The stained sections were examined by light microscopy and assigned a histologic score without knowledge of treatment category by an expert in cardiac pathology. The following scoring system of the myopathic change adopted from Bristow et al (Bristow et al. 1981; Bristow et al. 1980) was used: Grade 0=normal myocardium, no Adriamycin effect; Grade I=occasional sparse numbers of foci of vacuolated myocytes and/or minimal interstitial fibrosis; Grade II=moderate number of focal myocytes showing vacuolization and/or myofibril loss; Grade III=many generalized affected myocytes showing vacuolization and diffuse interstitial fibrosis.

Statistical analysis of the data was performed using unpaired Student's t test and Spearman's rank correlation coefficient test for nonparametric data (Snedecor and Cochran 1976).

RESULTS

The biodistribution of ^{111}In-AMAb, in control and Adriamycin-treated groups, expressed as % injected dose/gram tissue(%ID/gm) at 24 hours after injection for the heart and each organ, is shown in Table 1. The mean cardiac uptake of ^{111}In-AMAb was 0.021 in the control group and 0.056 in the Adriamycin-treated group. The difference between the two groups was significant($p<0.005$). The ratio of antibody accumulation of Adriamycin-treated over control rabbit based on the %ID/gm cardiac tissue was about 2.7:1. However, for other organs (lungs, kidneys, liver, spleen and bone) there was little difference between the two groups. Figure 1 presents the distribution of individual data of %ID/gm in each portion of the heart(left ventricle, right ventricle, septum and atrium). In all samples there was a significant increase of ^{111}In-AMAb accumulation in the Adriamycin-treated group compared with controls. Six of 10 rabbits treated with subtoxic doses of Adriamycin developed damaged hearts and had increased cardiac ^{111}In-AMAb activity which was greater than two standard deviations from the mean of control animals.

Table 2 and Figure 2 demonstrate the results of the biodistribution of ^{99m}Tc-pyrophosphate in control versus Adriamycin-treated treated animals in terms of %ID/gm tissue. Mean values of ^{99m}Tc-PYP uptake in the heart were 0.006 and 0.055 respectively ($p<0.05$). The distribution of individual data of %ID/gm tissue in each specimen of the heart revealed that 8 of 10 rabbits had an accumulation greater than 2 SD of the mean control value. In addition, the kidney and lung also showed significantly higher pyrophosphate uptake in Adriamycin-treated animals. The higher percent uptake of ^{99m}Tc-PYP in the kidney and lung may correlate with Adriamycin induced renal toxicity and congestive heart failure, respectively.

The histologic changes in the hearts of 15 Adriamycin treated animals were correlated with biodistribution results. As shown in Figures 3 and 4, qualitatively similar findings were observed in these rabbits. There was a strong relationship between both ^{111}In-AMAb and ^{99m}Tc-PYP uptake and the severity of myocardial damage by microscopic examinations. By Spearman's rank correlation coefficient (r) between ^{111}In-AMAb and histologic grading was 0.95 which was statistically significant ($p<0.001$) and better than the r value between ^{99m}Tc-PYP and histologic grading which was 0.77 with a statistical significance of $p<0.005$.

Interestingly, there were two rabbits in the

Table 1. Biodistribution of ^{111}In-antimyosin antibody in control and adriamycin-treated groups (Mean ± 1 SEM)

| Organ	% Dose/g tissue at 2 hrs after injection		p value
	Control (n=12)	Adriamycin (n=10)	
Heart	0.021 ± 0.002	0.056 ± 0.010	<0.005
Left Ventricle	0.020 ± 0.002	0.063 ± 0.010	<0.001
Right Ventricle	0.022 ± 0.003	0.052 ± 0.011	<0.01
Septum	0.021 ± 0.002	0.062 ± 0.012	<0.005
Atrium	0.023 ± 0.002	0.050 ± 0.009	<0.01
Lungs	0.028 ± 0.002	0.033 ± 0.003	NS
Kidneys	0.635 ± 0.069	0.697 ± 0.114	NS
Liver	0.106 ± 0.005	0.121 ± 0.011	NS
Spleen	0.115 ± 0.008	0.123 ± 0.017	NS
Rib	0.034 ± 0.007	0.027 ± 0.007	NS

NS; not significant
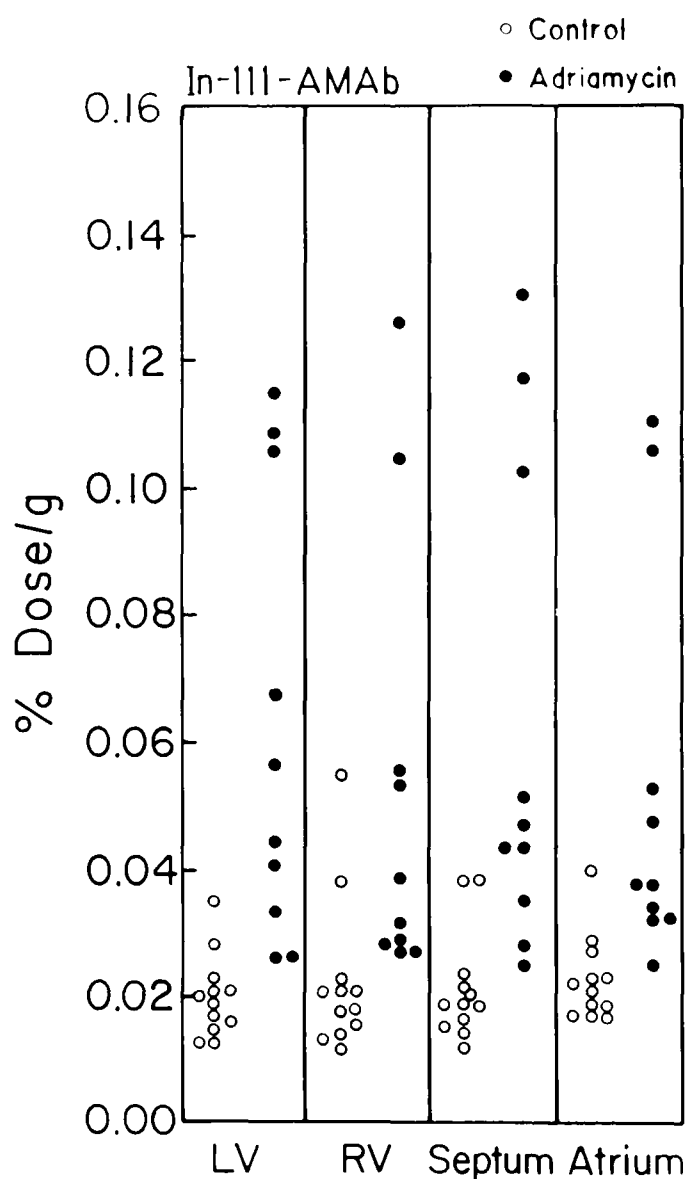
Fig. 1. Distribution of ^{111}In-AMAb (ID%/gm) in each portion of the heart.

Adriamycin treated group which showed normal PYP accumulation despite the abnormal histology and one rabbit that showed mild ^{111}In-AMAb uptake despite normal histology.

DISCUSSION

Doxocubicin hydrochloride (Adriamycin) has been clearly shown to be one of the most effective antitumor drugs in cancer chemotherapy (Bulum and Carter 1975; Benjamin et al. 1974). Its efficacy appears to depend on high cumulative dosages. However, the major dose-limiting side effect which is unique for this antibiotic is the development of dose related cardiotoxicity(doxorubicin cardiomyopathy) (Lefrak et al. 1973; Rinehart et al. 1974). The risk of heart failure has been reported to be negligible at total doses of less than 500 mg/m^2 (0.27%), but is much more likely to occur at doses above that level. The incidence of symptomatic congestive heart failure is approximately 10% of patients who received 550 to 660mg/m^2 and 35% of patients who received larger doses (more than 650mg/m^2) (Bristow 1982). Up to 50% of patients developing Adriamycin related congestive heart failure die of cardiac causes (Lefrak et al. 1975; Cortes et al. 1975). Jaenke (Jaenke 1976; Jaenke 1974) has described a similar myocardial syndrome from Adriamycin produced experime tally in rabbits. Gorton (Gorton et al. 1980) treated rabbits effectively with a dose of 14.4 mg/kg (158 mg/m^2), a level analogous to the 550 mg/m^2 described as the typically safe human dose.

The recognition of the earliest preclinical stages of doxorubicin induced cardiotoxicity must remain a goal for all physicians using this drug. So far, there is no reliable prediction of clinically significant doxorubicin induced cardiotoxicity. The morphologic changes observed in doxorubicin induced cardiotoxicity consist of: 1) cardiac dilatation and mural thrombosis; 2) degeneration and atrophy of cardiac muscle cells and 3) interstitial edema and fibrosis (Fervans 1978). The degeneration of myocardial cells can be characterized by myofibrillar loss and cytoplasmic vacuolization. As shown in this study, one striking finding is the wide range of histologic change and myocardial antimyosin antibody accumulation in the sub-toxic dose of Adriamycin-treated animals, suggesting differing individual sensitivity to Adriamycin. In fifteen animals examined by microscopy, six rabbits had developed mild myocardial lesions (Grade I), two moderate (Grade II) and only one severe (Grade III) at a total Adriamycin dose of 10 mg/kg. Recently cardiac imaging using radionuclide labeled compounds has proven useful for the detection

Table 2. Biodistribution of ^{99m}Tc-pyrophosphate (PYP) in control and adriamycin-treated groups (Mean ± 1 SEM)

Organ	% Dose/g tissue at 2 hrs after injection		p value
	Control (n=12)	Adriamycin (n=10)	
Heart	0.006 ± 0.0003	0.055 ± 0.022	<0.05
Left Ventricle	0.006 ± 0.0002	0.068 ± 0.027	<0.05
Right Ventricle	0.007 ± 0.0004	0.078 ± 0.037	<0.05
Septum	0.007 ± 0.0003	0.046 ± 0.018	<0.05
Atrium	0.008 ± 0.0004	0.039 ± 0.012	<0.01
Lungs	0.010 ± 0.001	0.016 ± 0.002	<0.005
Kidneys	0.209 ± 0.018	0.487 ± 0.078	<0.005
Liver	0.008 ± 0.001	0.014 ± 0.004	NS
Spleen	0.008 ± 0.001	0.014 ± 0.004	NS
Rib	0.074 ± 0.018	0.041 ± 0.009	NS

NS; not significant
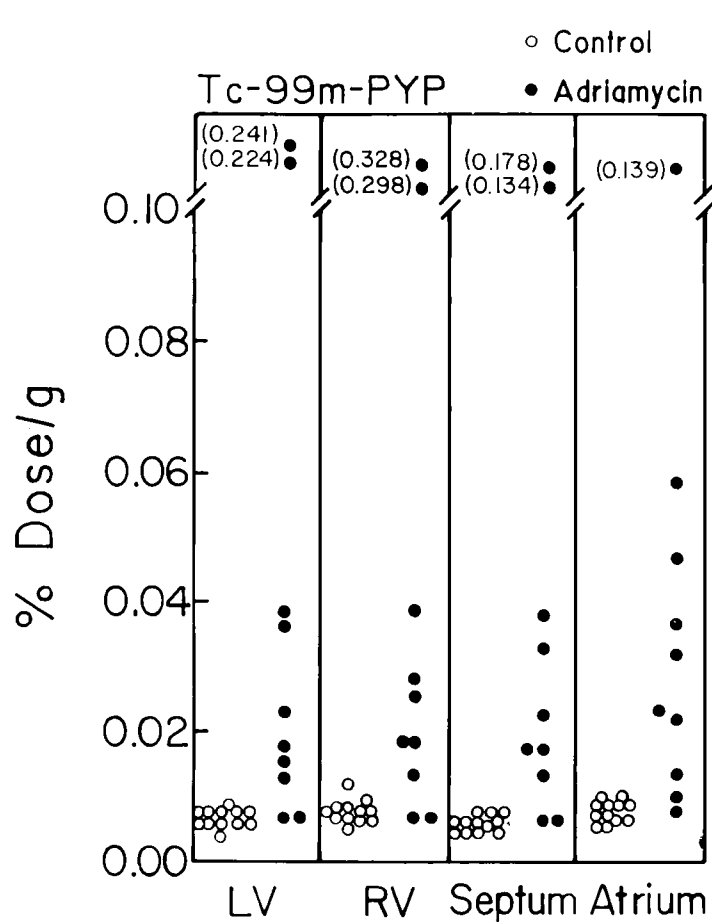
Fig. 2. Distribution of ^{99m}Tc-PYP (ID%/gm) in each portion of the heart.

Fig. 3. Correlation between the histologic changes and biodistribution results (ID%/gm) of ^{111}In-AMAb.

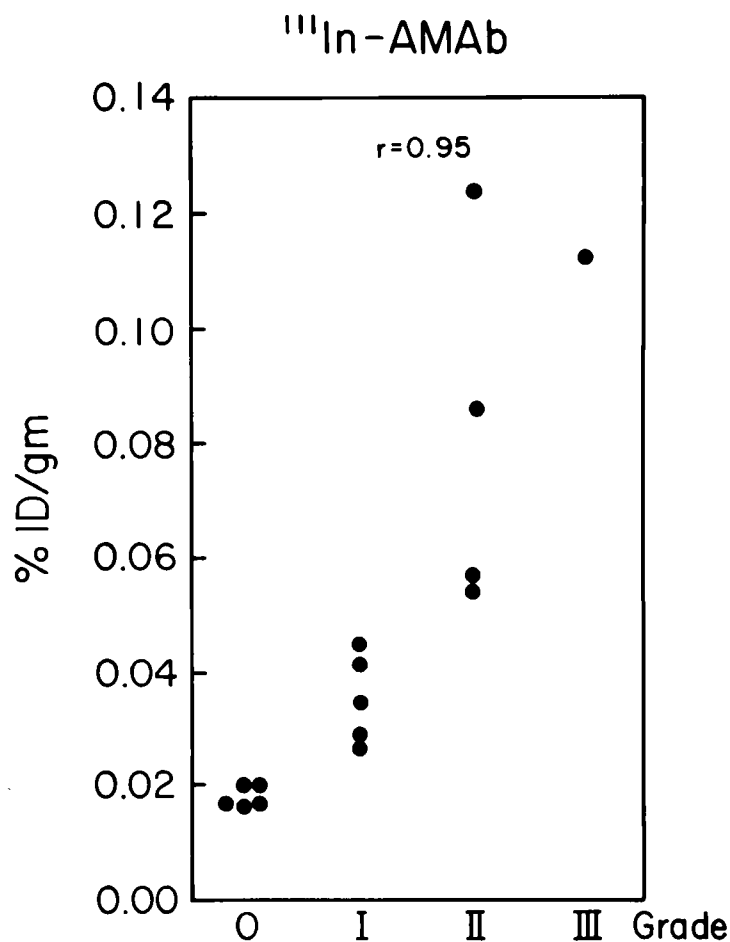of myocardial injury. Localization and sizing of acute myocardial infarcts have been done successfully with ^{99m}Tc-tetracycline (Holman *et al.* 1973), ^{99m}Tc-glucoheptonate (Rossman *et al.* 1975) and ^{99m}Tc-pyrophosphate (Parkley *et al.*
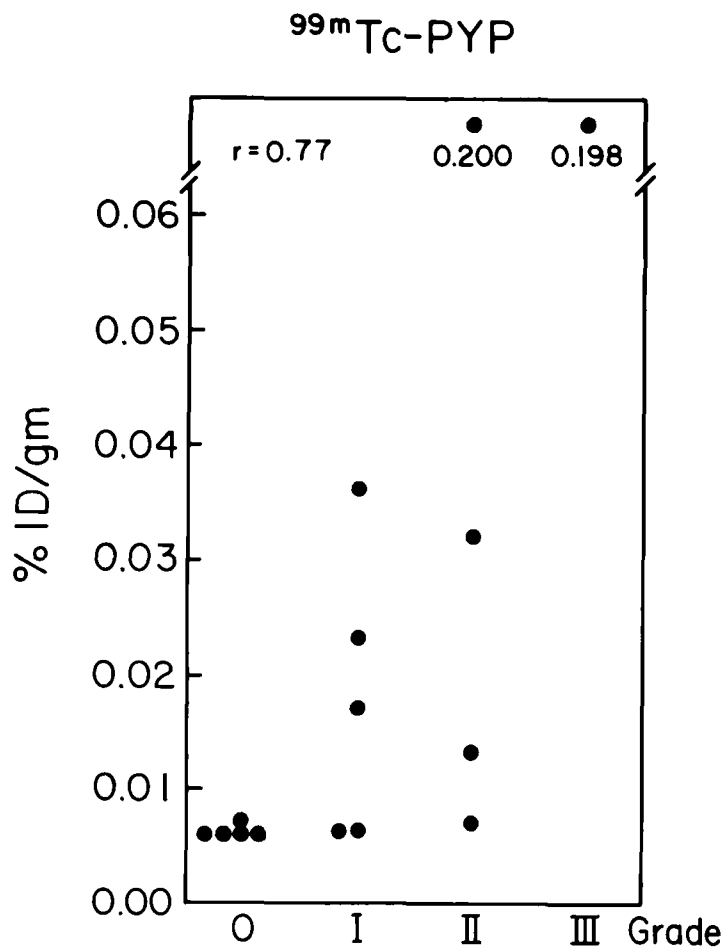
99mTc-PYP

Fig. 4. Correlation between the histologic changes and biodistribution results (ID%/gm) of ^{99m}Tc-pyrophosphate

1974; Coleman et al. 1976). Although the exact mechanism of accumulation of ^{99m}Tc-PYP has not been completely defined, it appears to be due in part to the PYP's binding to intracellular components via injured myocardial cell membrane allowing PYP to accumulate in the form of hydroxyapatite-like crystals in mitrochondria. This is often associated with cell necrosis and intracellular calcium accumulation (Buja et al. 1977). Some investigators (Gorton et al. 1980; Chacko et al. 1977) have reported that myocardial scanning using ^{99m}Tc-PYP may prove to be a valuable diagnostic tool in monitoring the adverse effects of the Adriamycin. They were able to detect myocardial damage before its clinical appearance. In our study ^{99m}Tc-PYP increasingly accumulated in hearts with Grade 0-III pathology, indicating that this agent can be utilized in staging Adriamycin cardiotoxicity.

More recently Khaw and others (Khaw et al. 1976; Khaw et al. 1978; Khaw et al. 1980; Beller et al. 1977; LaFrance et al. 1985; Takeda et al. 1985) localized myocardial infarcts by using radiolabeled antibodies to cardiac myosin. After intravenous injection of radioiodine-labeled fragments of antibodies that are specific for cardiac myosin, ratios of up to 6:1 between infarcted and normal myocardium were found in animal models. This ratio increased to greater than 20:1 in reperfused myocardial infarctions. Early studies (Khaw et al. 1978) used (Fab')2 while more recent studies used a Fab fragment antibody. With both, (Fab')2 and Fab, there was an inverse relationship between regional myocardial blood flow and uptake of the tracer. Similar results using ^{111}In-AMAb have been previously reported by our group and other investigators(LaFrance et al. 1985; Chacko et al. 1977).

In this study we measured the distribution of ^{111}In-antimyosin monoclonal antibody in myocardium of control rabbits and of animals treated with Adriamycin and we compared these results with those of ^{99m}Tc-pyrophosphate accumulation and correlated these results with radiopharmaceutical accumulation histologic findings in the same animals. Whether the ratio of ^{111}In-AMAb accumulation between Adriamycin treated and control rabbits in this study at 24 hours after intravenous injection was due only to lack of specificity of the antibody or was due to other factors was not studied.

The specificity of the human R11D10 antibody towards rabbit tissue also has not been previously evaluated. Investigations in dogs, however, have shown that the affinity of this antibody towards infarcted dog heart was similar to that of humans (Khaw et al. 1976).

The use of control rabbits along with histological and PYP comparison of our data revealed that there is some cross reactivity of the rabbit myosin with R11D10 murine antibody directed against human myosin. Since considerable similarities in mammalian myosin structure exist, cross reactivity was unexpected.

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Based upon our canine infarction work(LaFrance *et al.* 1985), the ratio of ^{111}In-AMAb accumulation in human myocardium damaged by Adriamycin may be similar to those higher ratios since better specificity of R11D10 AMAb exists for human myosin as compared to rabbit myosin.

Whether ^{111}In-AMAb levels in Adriamycin damaged myocardium resulting in myocardial necrosis will be greater in humans requires further study.

Using this experimentally induced rabbit model and ^{111}In-antimyosin antibody, we were able to detect increased myocardial uptake before clinical appearance. Statistically significant increased accumulation of radioactivity occurred even though these animals had been treated with what had previously been described as a sub-toxic dosage of Adriamycin (10mg/kg), levels previously expected to cause no cardiotoxicity.

The significant correlation between the ^{111}In-AMAb in the myocardium will occur at the stage when the damage is still at the cellular level rather than at the global organ level and it may prove to be a valuable tool in monitoring the adverse effects of the anthracycline antibiotics in patients.

In conclusion, this study has demonstrated that(Khaw *et al.* 1976) ^{111}In-AMAb accumulation in the heart correlated better than PYP with the degree of pathology (r=0.95); (Khaw *et al.* 1978) ^{99m}Tc-PYP uptake was also dependent on degree of cardiac damage (r=0.77); and (Parkley *et al.* 1974) however, the more favorable ratio of %ID/gm in the myocardium of treated animals occurred for ^{99m}Tc-PYP than for ^{111}In-AMAb to detect Adriamycin induced cardiac damage before the end stage of cardiac toxicity develops. This study supports the need for a similar study in humans to determine the relative advantages of ^{111}In-AMAb, ^{99m}Tc-PYP and histology.

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