Technetium-99m Pyrophosphate Uptake in Spontaneously Occurring Perimyocardial Lesions in an Inbred Strain of DBA/2 Mice

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The spontaneous occurrence of perimyocardial calcification localized in the right ventricle has been reported in an inbred strain of DBA/2 mice. In this paper we examined the correlation between the myocardial uptake ratio of technetium-99m pyrophosphate ($^{99m}\text{Tc-PYP}$) and pathological findings in these mice ranging in age from one to 12 months. The $^{99m}\text{Tc-PYP}$ myocardial uptake ratio was highest at 2 months and became lower with age, while calcification and fibrosis in the perimyocardium of the right ventricle became more prominent in aged mice. This may be due to an insidious onset of degeneration with calcification and fibrosis in spontaneously occurring perimyocardial lesions in these mice. Persistent abnormal uptake of $^{99m}\text{Tc-PYP}$ observed in the present study suggests the usefulness of such scintigrams in the diagnosis of chronic perimyocardial disease.

MYOCARDIAL imaging with technetium-99m pyrophosphate ($^{99m}\text{Tc-PYP}$) has been applied in the diagnosis of acute myocardial infarction.^{1,2} However, abnormal myocardial uptake of $^{99m}\text{Tc-PYP}$ may occur in various clinical conditions other than acute myocardial infarction, such as unstable angina, left ventricular aneurysm, myocardial contusion, cardiomyopathy, experimental myocarditis and clinical perimyocarditis in humans.³⁻⁸ It has been reported that spontaneous perimyocardial lesions with calcification localized in the right ventricle occurs in an inbred strain of DBA/2 mice. In order to evaluate the significance of an abnormal myocardial uptake of $^{99m}\text{Tc-PYP}$ in perimyocardial diseases, the correlation between the $^{99m}\text{Tc-PYP}$ myocardial uptake ratio and pathological findings was studied using these DBA/2 mice.

MATERIALS AND METHODS

Mice. Inbred strain of DBA/2 mice were obtained from the Shizuoka Agricultural Cooperative Association, Japan. This strain has been maintained continuously by brother-sister matings and mice ranging in age from one to 12 months were used in the present study. They were fed with a stock commercial ration consisting of approximately 21.3% protein, 6% fat, 55.9% carbohydrate, and containing adequate amounts of vitamins and minerals. Housing and care of the mice were made optimum.

Radiopharmaceuticals. Ten μCi of $^{99m}\text{Tc-PYP}$ was injected intravenously through a tail

Key Words:

Technetium-99m pyrophosphate
Spontaneous perimyocardial calcification
DBA/2 mice

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This work was supported in part by a Research Grant for the study of Intractable Diseases from the Ministry of Health and Welfare, and by Grants 56770426 and 56440045 from the Ministry of Education, Japan.

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Fig.1. Spontaneous perimyocardial calcification on the right ventricular surface in a DBA/2 mouse of 2 months of age. Hematoxylin and eosin stain, $\times 14$.

Fig.2. Higher magnification of Fig. 1. Microscopic lesions consisted of focal necrosis, fibrosis and diffuse calcification of the perimyocardium. $\times 120$

vein. Sixty min after the injection, animals were sacrificed by exsanguination and their hearts were excised and weighed. Radioactivities of the

heart and blood were counted using a well-scintillation counter. The ^{99m}Tc -PYP myocardial uptake ratio ($[\text{cpm}/\text{mg of the heart}]/[\text{cpm}/\text{ml of}$

Fig.3. ^{99m}Tc -PYP myocardial uptake ratio in an inbred strain of DBA/2 mice with perimyocardial lesions, ranging in age from one to 12 months. M = months of age

TABLE I INCIDENCE OF SPONTANEOUSLY OCCURRING MYOPERICARDIAL LESIONS IN DBA/2 MICE

Age (month)	Number of positive lesions (%)	
	Number of examined	
1	2/14 (14%)	
2	14/29 (48%)	
3	4/9 (44%)	
6	6/7 (86%)	
12	10/12 (83%)	

blood]) was calculated.

Histological examination. Tissues were fixed in 10% formalin, sectioned transversely at the midportion of the ventricle, embedded in paraffin and stained with hematoxylin and eosin and von Kossa stains.

RESULTS

On gross observation, perimyocardial calcification appeared as irregular, chalky white patches on the right ventricular surface (Fig. 1). Microscopic lesions such as focal necrosis, fibrosis and diffuse calcification of the perimyocardium were

observed (Fig. 2). The incidence of spontaneously occurring perimyocardial lesions with calcification in an inbred strain of DBA/2 mice was as follows: 2/14 (14%) at one month of age, 14/29 (48%) at 2 months, 4/9 (44%) at 3 months, 6/7 (86%) at 6 months and 10/12 (83%) at 12 months (Table I). Despite the presence of such perimyocardial lesions, these mice did not develop right ventricular failure and their growth was similar to that of the control group. The mean ^{99m}Tc -PYP myocardial uptake ratio was highest at 2 months of age as compared with the age-matched control ($p < 0.001$) and became lower with age. Although this ratio at 12 months was lower than that at 2 or 3 months ($p < 0.02$), it was still significantly higher as compared with that in the control group ($p < 0.001$) (Fig. 3).

DISCUSSION

Spontaneous calcification in the hearts of DBA/2 mice has been reported by Nabors⁹ and Eaton.¹⁰ Our experimental models used in the present study showed a high myocardial uptake ratio of ^{99m}Tc -PYP at 2 months of age and a gradual decrease of this ratio with age. However, perimyocardial calcification and fibrosis of the right ventricle became more prominent with age.

The ^{99m}Tc -PYP myocardial uptake ratio and pathological findings were similar to those in chronic perimyocarditis observed previously using BALB/c mice.¹¹ However, in our previous study of acute perimyocarditis using BALB/c mice,¹¹ the ^{99m}Tc -PYP myocardial uptake ratio increased more rapidly and reached higher levels of approximately 10 times as compared to those in the present models. These findings may be due to an insidious onset of degeneration accompanying necrosis and calcification in the spontaneously occurring perimyocardial lesions in an inbred strain of DBA/2 mice used in the present study.

The mechanism of ^{99m}Tc -PYP accumulation in the damaged myocardium is considered to be related to the formation of polynuclear complexes in a denatured myocardium,¹² or to the concentration of the substances which have been compounded with various soluble and insoluble forms of tissue calcium stores, such as amorphous calcium combined with organic macromolecules.¹³

Positive ^{99m}Tc -PYP myocardial scintigrams have been reported in idiopathic calcified constrictive pericarditis⁷ and in intense and persistent perimyocarditis in humans.⁸ The present results may provide an experimental evidence for positive ^{99m}Tc -PYP myocardial scintigrams in chronic calcified perimyocarditis.

REFERENCES

1. BONTE FJ, PARKEY RW, GRAHAM KD, MOORE J, STOKEY EM: A new method for radionuclide imaging of myocardial infarcts. *Radiology* 110: 473, 1974
2. WILLERSON JT, PARKEY RW, BONTE FJ, MEYER SL, ATKINS JA, STOKEY EM: Technetium stannous pyrophosphate myocardial scintigrams in patients with chest pain of varying etiology. *Circulation* 51: 1046, 1975
3. KADOTA K, MATSUMORI A, KAMBARA H, KAWAI C: Myocardial uptake of technetium-99m stannous pyrophosphate in experimental viral myopericarditis. *J Nucl Med* 20: 1047, 1979
4. MATSUMORI A, KADOTA K, KAWAI C: Technetium-99m pyrophosphate uptake in experimental viral perimyocarditis: Sequential study of myocardial uptake and pathologic correlates. *Circulation* 61: 802, 1980
5. SINGH A, USHER M, RAPHAEL L: Pericardial accumulation of Tc-99m methylene diphosphate in a case of pericarditis. *J Nucl Med* 18: 1141, 1977
6. DESA'NETO A, BULLINGTON JD, BULLINGTON RH, DESSER KB, BENCHIMOL A: Coxsackie B5 heart disease: Demonstration of inferolateral wall myocardial necrosis. *Am J Med* 68: 295, 1980
7. OLSON HG, LYONS KP, ARONOW WS, KUPERUS J, ORLANDO JR, WATERS HJ: Technetium-99m stannous pyrophosphate myocardial scintigrams in pericardial disease. *Am Heart J* 99: 459, 1980
8. AHMAD M, DUBIEL JP: Tc-99m pyrophosphate myocardial imaging in pericarditis. *J Nucl Med* 22: 452, 1981
9. NABORS CE, BALL CR: Spontaneous calcification in hearts of DBA mice. *Anat Res* 164: 153, 1969
10. EATON GJ, CUSTER RP, JOHNSON FN, STABENOW KT: Dystrophic cardiac calcinosis in mice. *Am J Pathol* 90: 173, 1978
11. MATSUMORI A, KAWAI C: Coxsackie virus B3 perimyocarditis in BALB/c mice: Experimental model of chronic perimyocarditis in the right ventricle. *J Pathol* 131: 97, 1980
12. DEWANJEE MK, KAHN PC: Mechanism of localization of ^{99m}Tc -labeled pyrophosphate and tetracycline in infarcted myocardium. *J Nucl Med* 17: 639, 1976
13. BUJA LM, TOFE AJ, KULKARNI PV, MUKHERJEE A, PARKEY RW, FRANCIS MD, BONTE FJ, WILLERSON JT: Sites and mechanisms of localization of technetium-99m phosphorus radiopharmaceuticals in acute myocardial infarcts and other tissues. *J Clin Invest* 60: 724, 1977