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Sequential change of BMIPP uptake with age in spontaneously hypertensive rat model

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Changes in myocardial perfusion and metabolism are often associated with myocardial hypertrophy, but there are few reports describing the serial assessment of fatty acid metabolism in hypertrophic myocardium. The aim of this study is to assess fatty acid metabolism serially in hypertrophic myocardium in spontaneously hypertensive rats (SHR) with ^{125}I-BMIPP, a branched fatty acid analog. *Methods:* SHR and Wistar-Kyoto rats (WKY) as the control were divided into 4 groups (12, 15, 18 and 51 weeks after birth). The heart was extracted 10 minutes after intravenous injection of ^{125}I-BMIPP and ^{201}Tl at the same time. The accumulation of each radiotracer in the myocardium was counted with a well gamma counter. In addition, ^{125}I-BMIPP uptake was corrected by ^{201}Tl uptake (B/T). *Results:* The heart weight/body weight ratio was significantly higher in SHR than that in WKY ($p < 0.001$). In SHR, this ratio increased up to 18 weeks (12 weeks; 0.266 ± 0.005, 18 weeks; 0.281 ± 0.006: mean ± SE, $p < 0.05$). The ^{125}I-BMIPP uptake tended to be significantly reduced in SHR (12 weeks; 2.373 ± 0.212, 18 weeks; 1.380 ± 0.047: mean ± SE, $p < 0.05$). Such a difference in BMIPP uptake was more evident when BMIPP uptake was corrected by Tl uptake (B/T), but no regional difference or heterogeneity of BMIPP distribution was observed in the hypertrophic myocardium in SHR. *Conclusion:* A change in fatty acid metabolism with age was observed in association with myocardial hypertrophy in this hypertensive rat model, which was well demonstrated with ^{125}I-BMIPP and ^{201}Tl.

Key words: hypertensive rat, myocardial hypertrophy, BMIPP, fatty acid metabolism

INTRODUCTION

IT HAS BEEN REPORTED that sustained hypertension causes structural and functional cardiac abnormalities that lead to myocardial ischemia, congestive heart failure, and sudden cardiac death.[1,2] On the other hand, it is well known that chronic hypertension often causes left ventricular hypertrophy and myocardial damage.[1,3,4] For these reasons, early detection and early treatment for hypertension is important. There are a variety of examinations such as electrocardiography, echocardiography and radionuclide imaging to clinically assess myocardial abnormalities.

Hypertension has been also studied basically, and many kinds of experimental hypertensive models have been developed to elucidate a mechanisms of hypertension and pathophysiology of myocardial hypertrophy.[5–13] A spontaneously hypertensive rat model (SHR) is one hypertensive animal model which is often used in the study of left ventricular hypertrophy.[9,11–13]

Radionuclide imaging is a useful means to identify regional perfusion and metabolic abnormalities. Recently, radioiodinated 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) was developed as a myocardial fatty acid metabolism imaging agent.[14,15] BMIPP is a methyl branched-chain fatty acid which is trapped in myocardial cells without being further metabolized by beta-oxidation, and by means of it regional myocardial fatty acid utilization can be assessed *in vivo*.[16–22]

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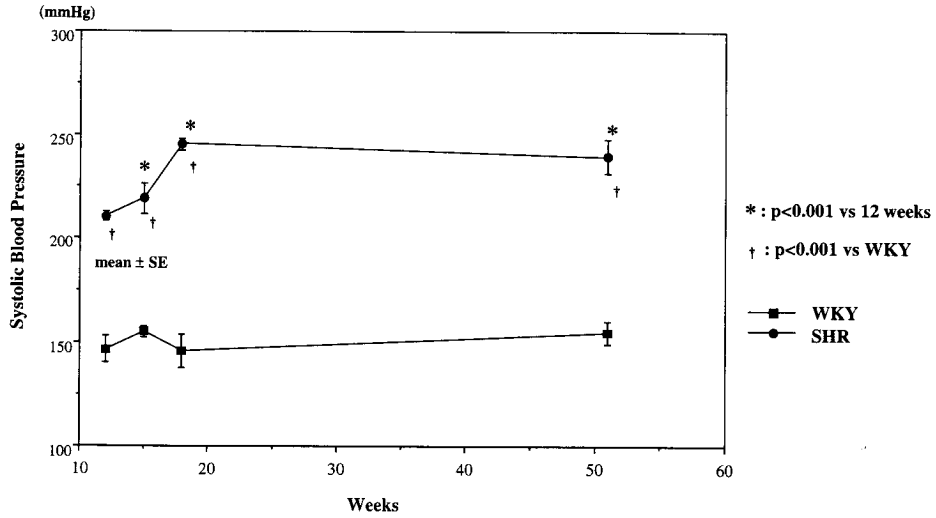

Fig. 1 The systolic blood pressure of SHR and WKY.

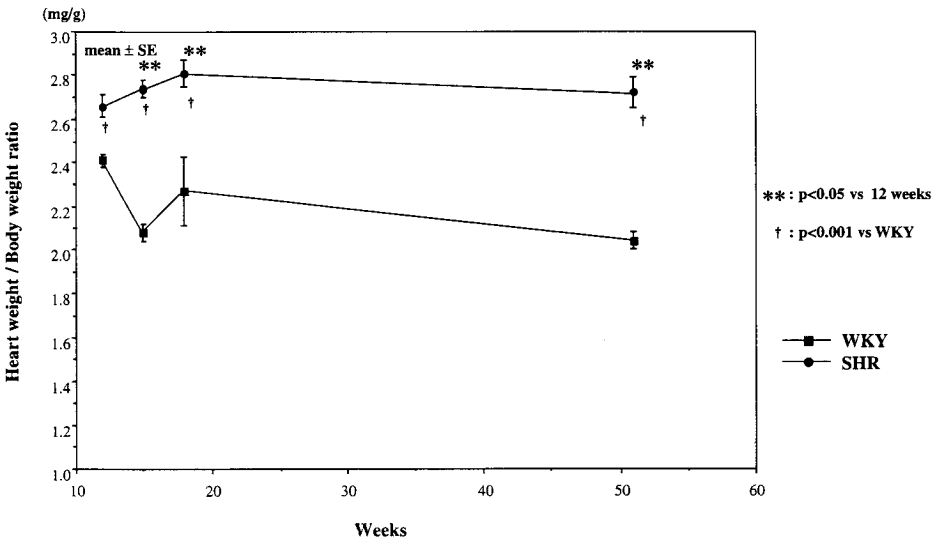

Fig. 2 The ratio of heart weight and body weight.

While a number of studies have been focused on the hypertrophic myocardium in cardiomyopathy[23-33] with use of this tracer, there were few studies to assess metabolic abnormality in the hypertrophic myocardium due to chronic hypertension. The aim of this study is to elucidate the characteristics of fatty acid metabolism in the hypertrophic myocardium in the SHR model by means of ^{125}I-BMIPP (BMIPP) and to relate them to fatty acid metabolism and perfusion.

METHODS

Animals

SHR were used as a hypertensive model and Wistar-Kyoto rats (WKY) as the control. They were divided into four groups: 8 SHR and 8 WKY were bred until 12 weeks old, 8 of each until 15 weeks old, 8 of each until 18 weeks old, and 5 SHR and 6 WKY until 51 weeks old. They were fed a normal pellet diet with water.

Radiotracers

BMIPP and ^{201}TlCl (Tl) were obtained from Nihon Medi-Physics Co., Ltd., Chiba, Japan.

Method of preparation of BMIPP: commercially obtained BMIPP (Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan), was labeled with iodine-125 by isotope exchange reaction with formic acid as a solvent and $CuSO_4$ as a catalyst. The specific activity ranged between 38.2 and 46.6 GBq/mmol. The crude product was purified by solvent extraction, and identified by thin layer chromatography. The radiochemical purity of this purified product was more than 95%. The labeled product was evaporated and dissolved in a 7 mg /ml ursodeoxycholic acid solution. The solution was finally sterilized by mil-

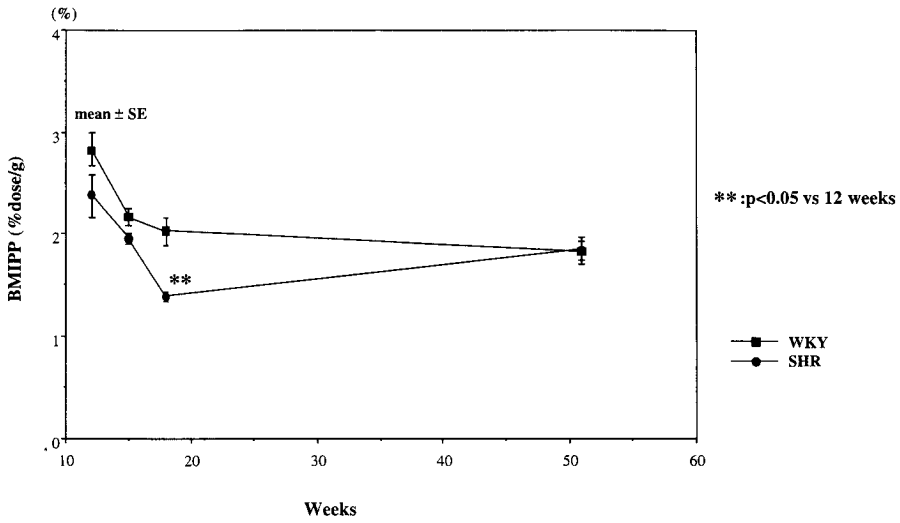

Fig. 3 The myocardial uptake of ^{125}I-BMIPP.

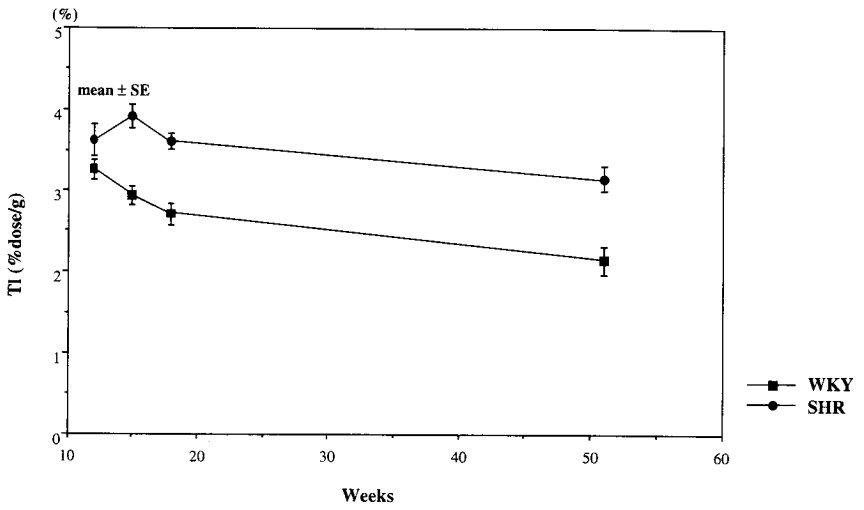

Fig. 4 The myocardial uptake of ^{201}Tl.

lipore (0.22 μm) filtration.

Study protocol

Blood pressure was measured by the tail cuff method, 12 hours before the study.

After a 12 hour fast, both SHR and WKY groups at the age of 12 weeks, 15 weeks, 18 weeks and 51 weeks old were injected intravenously with 0.37 MBq of BMIPP and 0.92 MBq of Tl at the same time.

The hearts were removed 10 minutes after injection, and divided into the right and left ventricle. The left ventricle was divided into 8 parts which were inner and outer myocardial regions of anterior, lateral, inferior and septal walls, respectively. The weight and Tl counts of all parts of the left ventricular myocardium were measured. Myocardial Tl counts and injected Tl counts were measured with an auto well counter (ARC-380, Aloca, Tokyo, Japan), with a set energy window of 60–80 keV. Myocardial BMIPP counts and injected BMIPP counts were measured with a 20–40 keV energy window with the same auto well counter one month later to eliminate the effect of Tl counts by correcting for time decay. The radioactivity associated with each radionuclide in other radionuclide windows was determined by using reference standards and the resultant crossover corrections were applied to tissue samples containing both tracers. This was achieved by evaluating aliquots of the pure radionuclides individually and then combined to contribute the count rate in each counting window to determine the crossover contribution of each radionuclide in the other radionuclide windows.

All these procedures were performed at the Central Institute of Isotope Science, Hokkaido University.

Calculation of parameters

Heart tissue weight per body weight (mg/g) (H/B ratio)

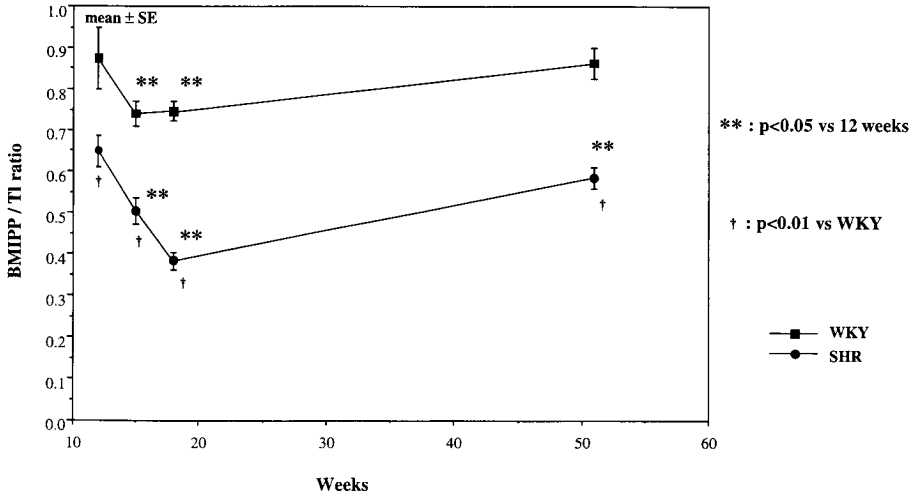

Fig. 5 The ratio of ^{125}I-BMIPP uptake and ^{201}Tl uptake.

Table 1 Outer and Inner myocardium tracer uptake

	BMIPP % dose/g	mean ± SE			
		12w	15w	18w	51w
WKY	Outer myocardium	2.818 ± 0.383	2.234 ± 0.083	1.994 ± 0.115	1.826 ± 0.138
	Inner myocardium	2.821 ± 0.176	2.066 ± 0.097	2.069 ± 0.166	1.839 ± 0.122
SHR	Outer myocardium	2.380 ± 0.203	1.964 ± 0.052	1.404 ± 0.049	1.873 ± 0.113
	Inner myocardium	2.361 ± 0.224	1.927 ± 0.054	1.346 ± 0.046	1.786 ± 0.084
	Tl % dose/g	mean ± SE			
		12w	15w	18w	51w
WKY	Outer myocardium	3.520 ± 0.089	3.136 ± 0.143	2.996 ± 0.208	2.297 ± 0.191
	Inner myocardium	3.034 ± 0.075	2.792 ± 0.163	2.409 ± 0.065	2.003 ± 0.145
SHR	Outer myocardium	3.804 ± 0.178	4.275 ± 0.176	3.840 ± 0.139	3.374 ± 0.149
	Inner myocardium	3.381 ± 0.163	3.809 ± 0.165	3.495 ± 0.091	3.110 ± 0.157
	BMIPP/Tl ratio	mean ± SE			
		12w	15w	18w	51w
WKY	Outer myocardium	0.935 ± 0.069	0.806 ± 0.036	0.826 ± 0.032	0.915 ± 0.037
	Inner myocardium	0.808 ± 0.065	0.663 ± 0.027	0.689 ± 0.015	0.813 ± 0.037
SHR	Outer myocardium	0.700 ± 0.038	0.527 ± 0.038	0.404 ± 0.023	0.605 ± 0.024
	Inner myocardium	0.616 ± 0.039	0.459 ± 0.030	0.355 ± 0.024	0.533 ± 0.037

was calculated as an index of myocardial hypertrophy. Percent uptakes of BMIPP and Tl in the left ventricular myocardium were calculated as follows:

(Tracer dose/g) = {(tissue counts of tracer) / (injected dose counts) × 100}/(tissue weight)

"Tracer" represents either BMIPP or Tl, while " tissue counts" and "injected dose counts" represent values obtained with a gamma counter.

In this study, we calculated (BMIPP % dose)/(Tl % dose) ratio (B/T ratio) as an index of the relationship between fatty acid metabolism and perfusion in the myocardium.

To assess regional uptake of the left ventricular myocardium, BMIPP and Tl uptake in the outer and inner myocardium as well as 4 different regions were compared. In addition, the coefficient of variation was calculated as a heterogeneity index.

Statistical analysis

All data were expressed as the mean plus or minus the standard error. Comparisons of uptake of tracers in the groups were performed with a combination of one way factorial ANOVA and Fisher's PLSD multiple comparison test. Two way factorial ANOVA was used for comparisons of SHR and WKY.

RESULTS

Blood pressure and ventricular hypertrophy

The systolic blood pressure (SBP) of SHR was higher than that of WKY in all weeks, especially in 12 weeks to

Table 2 Regional myocardial tracer uptake

	BMIPP % dose/g	mean ± SE			
		12w	15w	18w	51w
WKY	Anterior	5.959 ± 0.371	4.469 ± 0.218	4.173 ± 0.356	3.749 ± 0.254
	Lateral	5.694 ± 0.340	4.370 ± 0.162	4.252 ± 0.256	3.831 ± 0.267
	Inferior	5.634 ± 0.293	4.272 ± 0.137	3.981 ± 0.262	3.540 ± 0.240
	Septal	5.281 ± 0.362	4.186 ± 0.233	3.929 ± 0.262	3.572 ± 0.314
SHR	Anterior	4.814 ± 0.371	4.069 ± 0.095	2.874 ± 0.101	3.781 ± 0.224
	Lateral	4.940 ± 0.496	3.987 ± 0.118	2.807 ± 0.143	3.572 ± 0.160
	Inferior	4.658 ± 0.421	3.783 ± 0.124	2.720 ± 0.091	3.732 ± 0.228
	Septal	4.548 ± 0.435	3.712 ± 0.142	2.598 ± 0.095	3.674 ± 0.230
	Tl % dose/g	mean ± SE			
		12w	15w	18w	51w
WKY	Anterior	6.873 ± 0.185	5.995 ± 0.237	5.355 ± 0.233	4.292 ± 0.318
	Lateral	6.475 ± 0.160	5.888 ± 0.297	5.500 ± 0.277	4.307 ± 0.274
	Inferior	6.268 ± 0.161	5.852 ± 0.139	5.066 ± 0.211	4.153 ± 0.357
	Septal	6.654 ± 0.203	6.092 ± 0.331	5.868 ± 0.498	4.483 ± 0.402
SHR	Anterior	7.147 ± 0.299	8.464 ± 0.437	7.542 ± 0.235	6.586 ± 0.340
	Lateral	7.242 ± 0.363	8.212 ± 0.364	7.466 ± 0.219	6.403 ± 0.310
	Inferior	6.977 ± 0.356	7.696 ± 0.268	7.035 ± 0.268	6.397 ± 0.310
	Septal	7.493 ± 0.392	8.015 ± 0.366	7.375 ± 0.247	6.858 ± 0.359
	BMIPP/Tl ratio	mean ± SE			
		12w	15w	18w	51w
WKY	Anterior	0.875 ± 0.074	0.741 ± 0.030	0.746 ± 0.025	0.863 ± 0.035
	Lateral	0.886 ± 0.068	0.752 ± 0.037	0.776 ± 0.033	0.893 ± 0.040
	Inferior	0.906 ± 0.066	0.734 ± 0.032	0.784 ± 0.028	0.867 ± 0.041
	Septal	0.799 ± 0.067	0.691 ± 0.030	0.675 ± 0.019	0.804 ± 0.39
SHR	Anterior	0.650 ± 0.037	0.504 ± 0.032	0.384 ± 0.022	0.585 ± 0.026
	Lateral	0.678 ± 0.048	0.495 ± 0.034	0.378 ± 0.026	0.563 ± 0.025
	Inferior	0.664 ± 0.038	0.498 ± 0.029	0.392 ± 0.027	0.586 ± 0.028
	Septal	0.604 ± 0.039	0.473 ± 0.034	0.355 ± 0.020	0.538 ± 0.024

51 weeks ($p < 0.001$) (Fig. 1). In the SHR group, SBP increased with age up to 18 weeks ($p < 0.001$), but was unchanged over 51 weeks in the WKY group.

The heart weight/body weight ratio (H/B) of SHR was higher than that of WKY in all weeks ($p < 0.001$) (Fig. 2). In the SHR group, H/B increased with age from 12 weeks to 18 weeks ($p < 0.05$).

Radionuclide sequential changes

The BMIPP uptake tended to be decreased with age in both SHR and WKY groups (Fig. 3). In SHR, the BMIPP uptake was significantly decreased from 12 weeks (2.373 ± 0.212: mean ± SE) to 18 weeks (1.380 ± 0.047) ($p < 0.05$), but was unchanged from 18 weeks to 51 weeks (1.833 ± 0.093). The sequential change in the BMIPP uptake in WKY was similar to that in SHR, but not statistically significant. There was no statistically significant difference between SHR and WKY (12 weeks to 51 weeks).

The Tl uptake of SHR and WKY also tended to decrease with age (Fig. 4), but there was no statistically significant difference in SHR.

The B/T ratio was decreased in both groups from 12 weeks to 18 weeks ($p < 0.05$) (Fig. 5). At 51 weeks, on the other hand, the ratio was higher than at 18 weeks ratio in both group ($p < 0.05$).

Comparison of radionuclide uptake in SHR versus in WKY

Although the BMIPP uptake in SHR tends to be lower and the Tl uptake in SHR tends to be higher than those in WKY, there was no significant difference between SHR and WKY, but the B/T ratio was significantly lower in SHR than in WKY (12 weeks to 51 weeks) ($p < 0.01$).

Regional differences

There was no significant difference between the inner and outer myocardial regions in both rat groups in tracer uptake (Table 1), and there was no significant change among myocardial regions (Table 2).

Coefficient of variation (CV) values for each tracer uptake were similar in all WKY and SHR age groups, and this value did not differ with age (Table 3).

Table 3 Coefficient of variation (CV) values of each tracer distribution

BMIPP % dose/g CV	CV mean ± SE			
	12w	15w	18w	51w
WKY	8.428 ± 0.557	9.780 ± 1.073	8.501 ± 1.180	7.867 ± 0.518
SHR	6.704 ± 0.587	7.718 ± 0.945	7.716 ± 1.004	6.994 ± 2.281
Tl % dose/g CV	CV mean ± SE			
	12w	15w	18w	51w
WKY	9.766 ± 0.493	11.001 ± 1.468	9.417 ± 0.408	8.993 ± 1.061
SHR	8.252 ± 0.502	9.413 ± 0.330	7.323 ± 0.726	9.003 ± 1.863
BMIPP/Tl CV	CV mean ± SE			
	12w	15w	18w	51w
WKY	11.670 ± 0.914	13.598 ± 0.843	11.585 ± 0.294	10.168 ± 1.412
SHR	10.276 ± 0.769	10.248 ± 0.788	10.243 ± 0.575	8.821 ± 0.979

DISCUSSION

The present study with the iodinated fatty acid analogue BMIPP and thallium-201 indicates that a change in fatty acid metabolism may be associated with myocardial hypertrophy and this may precede perfusion abnormality in the spontaneously hypertensive rat model.

Perfusion abnormality has been well demonstrated in the hypertrophic myocardium.[34–37] In addition, metabolic abnormality has been reported in the experimental models as well as patients with hypertension and hypertrophic cardiomyopathy.[38–40] An autoradiographic study demonstrated a decreased uptake of branched fatty acid compound relative to perfusion in the hypertrophic rat model,[6,8] but most of the studies have been performed with positron emitting tracers.

Recently, iodinated fatty acid compounds have been introduced to assess fatty acid metabolism. Among them, ^{123}I labeled iodopheyl pentadecanoic acid (BMIPP) has been developed to probe fatty acid utilization on the basis of the tracer uptake.[14,15] BMIPP enters in the lipid pool of the myocardium, and therefore, its uptake reflects myocardial fatty acid utilization.[16–22] Although the BMIPP distribution was generally similar to regional perfusion, it was occasionally reduced relative to thallium perfusion in the ischemic myocardium.[20,21] In the studies of patients with hypertrophic cardiomyopathy, it is often observed that myocardial BMIPP uptake is less than thallium perfusion, particularly in the hypertrophic myocardium,[23–33] but there are only a few reports showing abnormal BMIPP uptake in the hypertrophied myocardium in hypertensive heart disease.[27,31]

The present study indicated a decrease in BMIPP uptake relative to that of Tl in the hypertrophied myocardium in hypertensive rats. In addition, the sequential analysis showed a mild decrease in BMIPP uptake with age related to myocardial hypertrophy. Since these changes were rather homogeneous, *in vivo* BMIPP imaging may not identify such subtle changes. The thallium uptake, on the other hand, did not significantly change during 12–18 weeks in SHR, so that in this period the BMIPP/Tl ratio decreased sequentially in relation to myocardial hypertrophy in this model. In the chronic stage (age 51 weeks), thallium uptake decreased, but BMIPP uptake did not change, and this ratio therefore tended to be higher than at 18 weeks. The reason for these changes may be that the myocardial metabolic damage in hypertension occurred in the early phase up to 18 weeks, with no further change in the chronic phase up to 51 weeks, but the myocardial perfusion in the early phase was related to an increase in systolic blood pressure. The change in thallium uptake during 12–18 weeks in SHR may therefore reflect increased regional myocardial blood flow due to hypertension. On the other hand, since an elder SHR has fibrotic change in the myocardium,[41] the thallium uptake may decrease in the chronic phase, so that the combined imaging with BMIPP and Tl is considered to be useful in detecting early metabolic change in hypertrophic myocardium, and has often been used for other cardiac disorders.[9,24,26,30,31]

We could not find significant differences between epicardial and endocardial distributions of BMIPP, even in the chronic stage (51 weeks) of hypertension. This finding disagrees with a previous report indicating heterogeneous distribution of BMIPP in SHR (40 weeks) in an autoradiographic study.[9] In this study, we have only divided the left ventricular myocardium into eight global sections for tissue counting, not obtained an autoradiograph. The autoradiographic analysis may find more subtle changes in the tracer distribution. A more precise evaluation of tracer distribution in relation to individual findings may be needed in this respect.

Regional differences are well demonstrated in the early stage of different rat models.[6] Yonekura et al. nicely demonstrated a decrease in branched fatty acid uptake in the subendocardium and septal regions. Such discordant findings may come from the differences of the experimental rat models. Dahl strain rats may show more a rapid

change in blood pressure with a salty diet.[42] This rapid change in this model may cause more severe damage in subendocardial regions, whereas the currently used spontaneous hypertensive rat model may cause a rather slow process of myocardial damage due to chronic hypertension.[9,11,12] In the clinical setting, hypertension usually make a mild and chronic course for myocardial hypertrophy.[1,3,4] In this respect, the spontaneous hypertensive rat model may be more suitable for assess chronic alteraton of myocardial perfusion and metabolism. Similarly, the regional differences in BMIPP uptake may be rarely seen in hypertensive heart disease, despite a similar degree of hypertrophy. This may be due to concentric hypertrophy rather than asymmetrical hypertrophy which is often seen in patients with hypertrophic cardiomyopathy. A precise quantitation of BMIPP and thallium distribution might possibly identify alteraton of fatty acid metabolism in these patients.

Our data also indicate alteraton of BMIPP uptake with age in control rats. Although the changes were less significant than in spontaneous hypertensive rat model, BMIPP uptake tended to be reduced with age in the control rats. Such physiological changes should be taken into consideration for further experimental studies.

In conclusion, serial alteration of fatty acid metabolism is suggested in relation to myocardial hypertrophy with age in the spontaneously hypertensive rat model. Such changes can be well demonstrated with combined assessment of BMIPP and thallium. These analysis should be helpful for pathophysiological understanding of hypertrophic myocardium and treatment effects of a variety of anti-hypertensive agents in patients with systemic hypertension.

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