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Detection of impaired fatty acid metabolism in right ventricular hypertrophy: Assessment by I-123 β-methyl iodophenyl pentadecanoic acid (BMIPP) myocardial single-photon emission computed tomography

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Fatty acid metabolism has been reported to be impaired earlier than myocardial blood flow in left ventricular hypertrophic myocardium, e.g., in hypertrophic cardiomyopathy or hypertensive heart disease. The purpose of this study was to determine whether impaired fatty acid metabolism also occurs in right ventricular (RV) hypertrophy. The subjects consisted of 6 patients with chronic obstructive pulmonary disease, 4 with primary pulmonary hypertension, 2 each with refractory pulmonary tuberculosis, tricuspid insufficiency, pulmonary embolism, 1 each with atrial septal defect, ventricular septal defect (Eisenmenger complex), Ebstein anomaly, and endocardial defect, and 7 healthy controls. SPECT imaging with Tl-201 (Tl) and I-123 β-methyliodophenyl pentadecanoic acid (BMIPP), and Tc-99m RBC first pass and gated blood pool scintigraphy were performed. Based on Tl planar images, the subjects were classified into 3 groups: 7 patients with no RV visualization (Group A), 11 with moderate RV visualization (Group B) and 9 with marked RV visualization (Group C). As a semi-quantitative evaluation by Tl myocardial SPECT, 3 regions in 3 representative short axial images were divided into 9 segments, each of which was graded from 0 to +3, and their sum was calculated as the RV score. The right ventricular ejection fraction (RVEF) and the left ventricular ejection fraction were obtained by Tc-99m RBC cardiac scintigraphy. The groups with marked visualization of the right ventricle had lower RVEF ($p < 0.01$), and there was a good correlation between the RVEF and the RV score with both Tl and BMIPP (Tl: $r = -0.79$, BMIPP: $r = -0.70$). Although a good correlation was demonstrated between the RV score with Tl and BMIPP in Groups A and B ($r = 0.86$, $p < 0.001$), in Group C, in which there was marked RV Tl visualization, the RV score with BMIPP was significantly smaller than with Tl (BMIPP vs. Tl: 11.5 ± 3.7 vs. 16.4 ± 3.8, $p < 0.01$). These findings suggest that impaired fatty acid metabolism may exist in severely hypertrophic right ventricle due to RV overload.

Key words: I-123 BMIPP, Tl-201, right ventricular overload, SPECT, myocardium

INTRODUCTION

THE MAIN ENERGY SOURCES of the myocardium are fatty acids and glucose. Since β-oxidation of fatty acids is a highly efficient source of energy, healthy myocardium with a sufficient oxygen supply depends on fatty acid metabolism for more than 80% of its energy supply. Fatty acid metabolism in the myocardium has been conventionally estimated by measuring the level of lactic acid and oxygen consumption in blood samples from the coronary sinus.[1,2] Clinical application of I-123 β-iodophenyl pentadecanoic acid (BMIPP) has enabled evaluation of fatty acid metabolism by SPECT images. ^{201}Tl (Tl) and BMIPP myocardial SPECT studies in hypertrophic cardiomyopathy and hypertensive heart diseases have revealed that metabolic abnormalities precede the

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occurrence of blood flow abnormalities in hypertrophic left ventricular myocardium.[3-5] These findings indicate that BMIPP myocardial SPECT is useful for the early detection of lesions, or predicting outcome, and follow-up observation.[6-8]

Cohen et al.[9] were the first to use Tl myocardial scintigraphy to evaluate right ventricular overload, and since then many studies have demonstrated its usefulness. In the present study, BMIPP scintigraphy was performed on patients with heart disease who had right ventricular hypertrophy, and compared with Tl scintigraphy to examine whether BMIPP myocardial scintigraphy would be useful for evaluating right ventricular overload. We also investigated whether the impaired fatty acid metabolism often observed in the left ventricle might exist in hypertrophic right ventricular myocardium.

MATERIALS AND METHODS

Patient selection

The subjects were 20 patients with right ventricular hypertrophy secondary to right ventricular overload (9 men and 11 women, mean age: 65.5 ± 14.4 years) and 7 healthy controls (3 men and 4 women, mean age: 70.1 ± 3.2 years). There were 6 patients with chronic obstructive pulmonary disease, 4 with primary pulmonary hypertension, 2 each with refractory pulmonary tuberculosis, tricuspid insufficiency and pulmonary embolism, and 1 each with atrial septal defect, ventricular septal defect (Eisenmenger complex), Ebstein anomaly and endocardial defect.

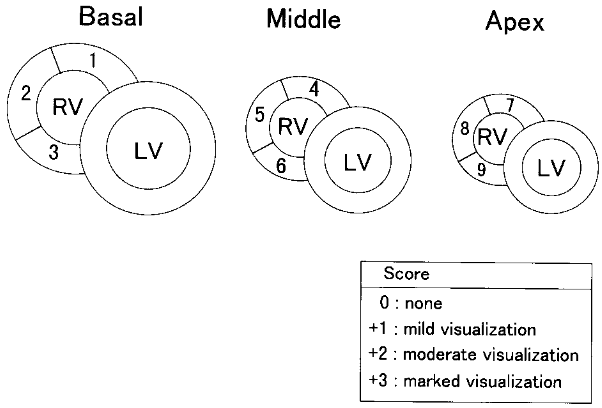

Fig. 1 Schematic representation of short-axis views at the basal, middle and apical levels of the right ventricle. LV = left ventricle, RV = right ventricle

Data acquisition

Under fasting conditions, Tl 74 MBq and BMIPP 111 MBq were intravenously injected on different days within one week, and planar and SPECT imaging were performed about 20 min after the injection. The best septal left anterior oblique (LAO) image was obtained at a preset time of 300 sec, and SPECT images were obtained during 180° rotation from 45° LAO to 45° right anterior oblique (RAO) at 25 sec at each step, and corrected for scattered radiation by the triple energy window method.[10] After intravenous injection of Tc-99m RBC (*in vivo* labeling) with 925 MBq, cardiac scintigraphy was performed at RAO 30° by the first pass method, then at the best septal LAO image was obtained by the multi-gated method.

Data analysis

The right ventricular ejection fraction (RVEF) was obtained by the first pass method, and the left ventricular ejection fraction (LVEF) by the multi-gated method. Based on the Tl planar images, the subjects were classified into 3 groups by the modified method of Cohen et al.,[9] and semi-quantitative evaluation of RV visualization by SPECT was performed. As shown in Fig. 1, the three regions of the basal, mid-ventricular, and apical short axial SPECT images were divided into 9 segments, each of which was graded from 0 to +3 (0: no visualization of the right ventricle, +1: slight visualization of the right ventricle, +2: visualization of the right ventricle but lower uptake than the left ventricular free wall, +3: visualization of the right ventricle and similar or higher uptake than the left ventricular free wall), and their sum was calculated to obtain right ventricular (RV) scores. The RV visualization was scored by three physicians in conference with no knowledge of the patients background.

Statistical analysis

The results are expressed as the means ± SD. Regression lines were calculated by the least-squares method. Differences between groups were examined by the one-way

Table 1 Patient characteristics

	Group A	Group B	Group C	p-value
No. of patients	7	11	9	
Age	70.1 ± 3.2	71.2 ± 7.8	58.6 ± 17.2	NS
RVEF	53.7 ± 6.1	37.6 ± 7.4	23.2 ± 8.2	p < 0.01
LVEF	60.9 ± 11.4*	51.0 ± 7.1	43.8 ± 11.5*	p < 0.05*
RV score (Tl)	1.6 ± 1.8	6.4 ± 2.1	16.4 ± 3.8	p < 0.001
RV score (BMIPP)	2.4 ± 2.8	7.2 ± 2.6	11.5 ± 3.7	p < 0.001

RVEF: Right ventricular ejection fraction, LVEF: Left ventricular ejection fraction, RV score: Right ventricular score

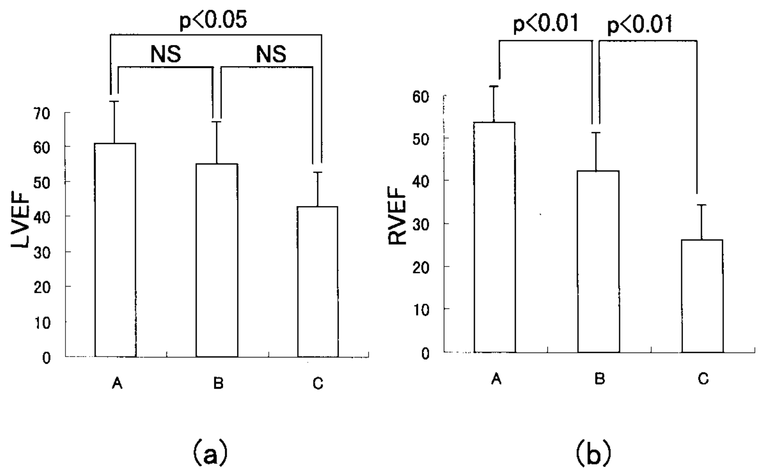

Fig. 2 Right ventricular ejection fraction (a) and left ventricular ejection fraction (b) in each group.

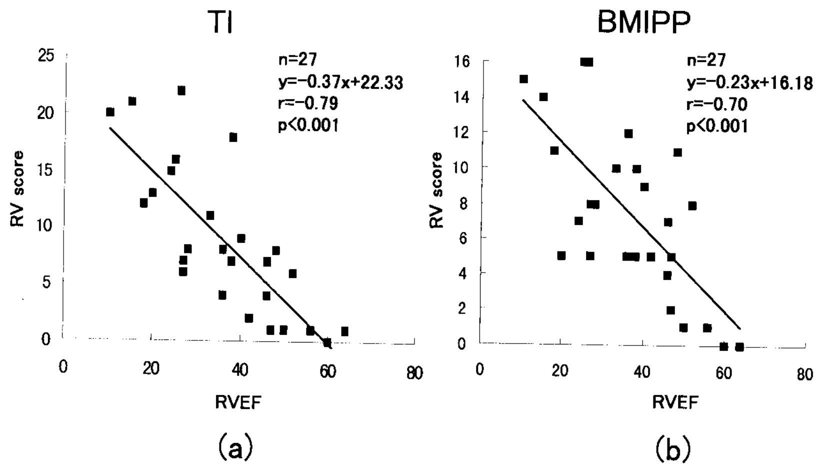

Fig. 3 Correlation between RV score and right ventricular ejection fraction by Tl myocardial SPECT (a) and BMIPP myocardial SPECT (b).

analysis of variance or Kruskal-Wallis test. Differences between Tl and BMIPP RV scores in each group were examined by the paired t-test. A value of $p < 0.05$ was considered significant.

RESULTS

Based on visual evaluation of Tl planar images, the subjects were classified into 3 groups as shown in Table 1. Group A consisted of 7 healthy subjects without visualization of the right ventricle; Group B consisted of 11 patients with visible images of the right ventricle at lower intensities than that of the left ventricle; and Group C consisted of the remaining 9 patients with a more prominent right ventricle image than the left ventricle image. Groups A, B and C were compared with regard to LVEF and RVEF (Fig. 2). The mean LVEF was 60.9 ± 11.4% in Group A, 51.0 ± 7.1% in Group B and 43.8 ± 11.5% in Group C, showing a tendency to a reduction toward Group C (Fig. 2a). Mean RVEF was 53.7 ± 6.1% in Group A, 37.6 ± 7.4% in Group B, and 23.2 ± 8.2% in Group C, with significantly lower values in the groups with clearer visualization of the right ventricle ($p < 0.01$, Fig. 2b). The relationship between the RVEF and the RV score was examined by Tl and BMIPP myocardial SPECT, and good negative correlations were found, with correlation coefficients of −0.79 with Tl and −0.70 with BMIPP (Fig. 3a, b). The RV scores for Tl and BMIPP were compared in all subjects. As shown in Fig. 4, there was a good correlation between Tl and BMIPP RV scores ($y = 0.6x + 2.29$, $r = 0.85$, $p < 0.001$). The Tl and BMIPP RV scores for each group were compared. The mean Tl vs. BMIPP RV scores were 1.6 ± 1.8 vs. 2.4 ± 2.8 in Group A, and 6.4 ± 2.1 vs. 7.2 ± 2.6 in Group B. The differences between the RV scores in these two groups were not significant, but, in Group C, which showed marked visualization of the right ventricle, the mean Tl vs. BMIPP RV scores were 16.4 ± 3.8 vs. 11.5 ± 3.7, with BMIPP showing a significantly smaller RV score ($p < 0.01$, Fig. 5).

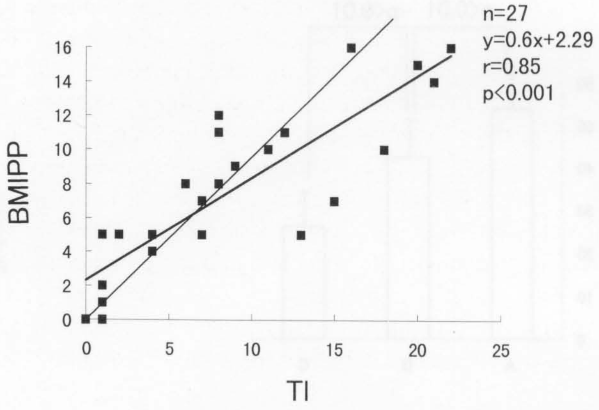

Fig. 4 Correlation between RV scores by Tl and BMIPP myocardial SPECT.

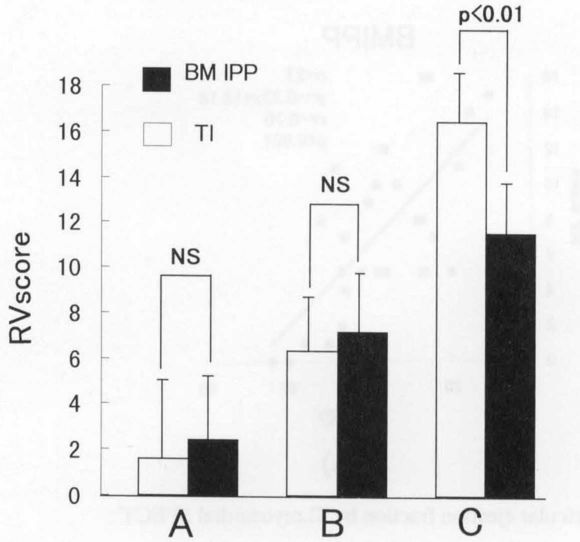

Fig. 5 Comparison between RV scores by Tl and BMIPP myocardial SPECT in each group.

Case report 1

The patient was a 47-year-old female with primary pulmonary hypertension. Mean pulmonary artery pressure was 74 torr, and systolic pressure in the right ventricle was 112 torr. RVEF was 26%. The right ventricular myocardium was significantly hypertrophic. The reduction in uptake at the apex of the right ventricle was assessed by BMIPP myocardial SPECT, and the results were clearly differed from those obtained by Tl myocardial SPECT (Fig. 6).

Case report 2

The patient was a 48-year-old female with primary pulmonary hypertension. Pulmonary artery pressure was 105/39 torr (mean, 67 torr), and the RVEF was 10%. There was less uptake in the free wall of the right ventricle in BMIPP myocardial SPECT than in Tl myocardial SPECT (Fig. 7).

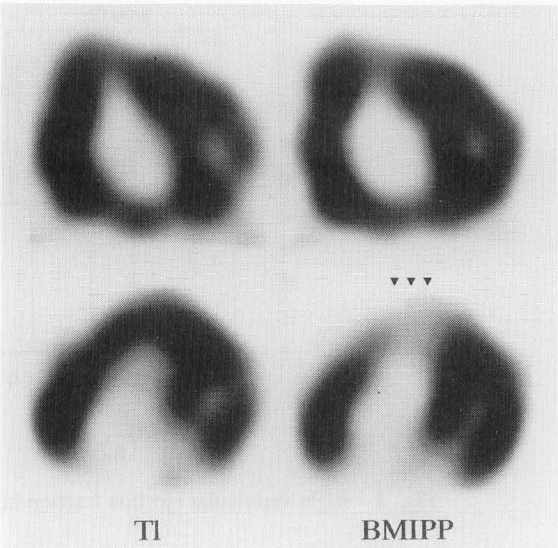

Fig. 6 Case 1. A 47-year-old female with primary pulmonary hypertension. The mean pulmonary artery pressure was 74 torr, and the right ventricular ejection fraction was 26%. The uptake in the apical right ventricular myocardium was reduced by BMIPP myocardial SPECT, compared with ^{201}Tl.

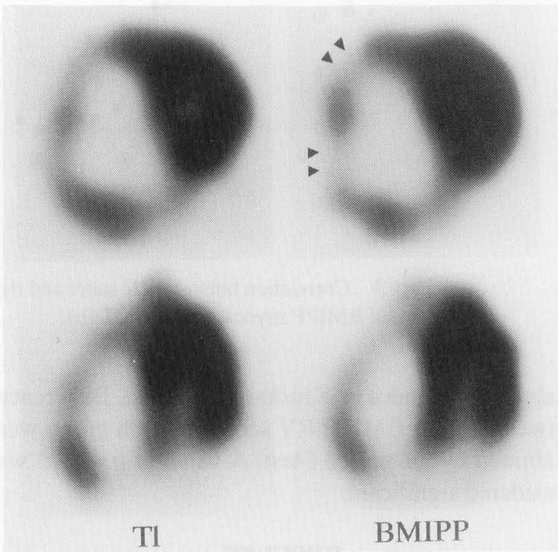

Fig. 7 Case 2. A 48-year-old female with primary pulmonary hypertension. Mean pulmonary artery pressure was 67 torr, and the right ventricular ejection fraction was 10%. Reduced BMIPP uptake was seen in the free wall of the right ventricle, compared with Tl.

DISCUSSION

Impaired fatty acid metabolism in the myocardium has been estimated by measuring the level of lactic acid and oxygen consumption in blood samples from the coronary sinus.[1,2] Basic studies and clinical application of BMIPP have enabled evaluation of fatty acid metabolism in the myocardium by means of SPECT images.[11–14] Tl and

BMIPP myocardial scintigraphic studies of the hypertrophic left ventricular myocardium in patients with hypertrophic cardiomyopathy and hypertensive heart diseases have revealed that the metabolic abnormalities in the hypertrophic myocardium precede the occurrence of abnormalities in the blood flow findings.[3–5] In particular, there have been reports showing that the reduction of BMIPP uptake at hypertrophic sites in hypertrophic cardiomyopathy reflects abnormal fatty acid metabolism, and it has been noted that this reduction in BMIPP uptake may be caused by the limitation of coronary flow reserve.[15–19] Furthermore, a reduction in IPPA uptake in hypertrophic left ventricular myocardium has also been reported.[20] These findings indicate that SPECT with fatty acid analogs is useful for early detection, and follow-up of hypertrophic myocardium.[6–9]

Cohen et al.[10] were the first to use Tl myocardial scintigraphy to evaluate right ventricular overload, and since then many studies have confirmed its usefulness.[21–23] Since RVEF obtained by the first pass method is closely correlated with right ventricular systolic pressure and mean pulmonary artery pressure, it can be assumed to be a parameter that reflects right ventricular after-load.[24–27] Thus, in the present study we used RVEF as a parameter of right ventricular after-load, and investigated whether BMIPP myocardial SPECT could be used to evaluate right ventricular overload as with Tl myocardial SPECT, and then assessed whether metabolic disorders could be detected earlier in the right ventricular myocardium by BMIPP. In diseases accompanied by abnormal right ventricular overload, BMIPP imaging of the right ventricle yielded a good negative correlation with RVEF, as does Tl, and thus BMIPP myocardial SPECT was considered useful in evaluating right ventricular overload. We examined many cases of pulmonary disease. All these patients belonged to Group B, and showed no reduction in BMIPP uptake. Because their blood oxygen saturation was over 90 percent with oxygen therapy, in this study we cannot argue that there is a relationship between the reduction in BMIPP uptake and a decline in blood oxygen saturation. Only in Group C, with marked visualization of the right ventricle, representing severe conditions according to the classification of Cohen et al., was the RV score with BMIPP smaller than with Tl, indicating a difference in uptake. In this group, right ventricular hypertrophy is concentric and a diffuse reduction in BMIPP uptake was seen in the free wall ventricle in many cases. RVEF declined successively in Groups A, B and C. Because the reduction in BMIPP uptake was demonstrated, the decline in right ventricular contractility may be therefore produced by both the after load and the impaired fatty acid metabolism.

In animal experiments, enlargement and hypertrophy of the right ventricle have been shown to occur secondary to an increase in pulmonary arterial pressure, leading to reduced coronary reserve function, a condition similar to ischemia.[31–33] Schulman et al.[34] tried to detect ischemia in hypertrophic myocardium of the right ventricle by Tl myocardial scintigraphy by using dipyridamole, but failed to reach definite conclusions, and suggested detecting ischemia by examining blood flow and metabolism in the right ventricle by means of positron emission tomography. The usefulness of BMIPP myocardial SPECT in ischemic heart disease and hypertrophic heart disease is well established.[13] Moreover, the reduction in BMIPP uptake in the right ventricular myocardium becomes marked in severely hypertrophic right ventricular myocardium, suggesting abnormal metabolism in the myocardium of the right ventricle. This may be due to hypertrophy of the myocardium itself or ischemia caused by both hypertrophic myocardium and the reduction in coronary flow reserve.

In conclusion, we succeeded in demonstrating these conditions in the right ventricle by metabolic imaging for the first time. Further studies are needed to investigate the difference in uptake of Tl and BMIPP in hypertrophic right ventricular myocardium in relation to pressure and volume overload.

REFERENCES

1. Most AS, Szydlik PA, Sorem KR. Effect of fatty acid on myocardial function during hypoxia. *Cardiology* 57: 322–332, 1972.
2. Ueda A, Su KM, Okabe F, Sada T, Ito T, Masumoto S, et al. Effect of right and left ventricular pressure overload on left ventricular function and metabolism in dogs. *Advances in Myocardiology* 2: 239–247, 1980.
3. Yonehara Y, Brill AB, Som P, Yamamoto K, Srivastava SC, Iwai J, et al. Regional myocardial substrate uptake in hypertensive rats. *Science* 227: 1494–1496, 1985.
4. Kurata C, Kobayashi A, Yamazaki N. Dual tracer autoradiographic study with thallium-201 and radioiodinated fatty acid in cardiomyopathic hamsters. *J Nucl Med* 30: 80–87, 1989.
5. Sago M, Nishimura T. Serial assessment of myocardial thallium perfusion and fatty acid utilization in spontaneously hypertensive rats: Assessment by autoradiography and pin-hole imaging. *KAKU IGAKU (Jpn J Nucl Med)* 26: 855–863, 1989.
6. Kurata C, Tawarahara K, Taguchi T, Aoshima S, Kobayashi A, Yamazaki N, et al. Myocardial emission computed tomography with iodine-123-labeled beta-methyl-branched fatty acid in patients with hypertrophic cardiomyopathy. *J Nucl Med* 33: 6–13, 1992.
7. Nishimura T, Nagata S, Uehara T, Morozumi T, Ishida Y, Nakata T, et al. Prognosis of hypertrophic cardiomyopathy: Assessment by ^{123}I-BMIPP myocardial single photon emission computed tomography. *Ann Nucl Med* 10: 71–78, 1996.
8. Nakai K, Ahmad M, Nakaki M, Wilkinson R, Callaham RJ, Elmaleh DR, et al. Serial course of left ventricular function, perfusion and fatty acid uptake in the cardiomyopathic hamster. *J Nucl Med* 34: 1309–1315, 1993.
9. Cohen HA, Baird MG, Rouleau JR, Ruhmann F, Bailey IK,

Summer WR, et al. Thallium-201 myocardial imaging in patients with pulmonary hypertension. *Circulation* 54: 790–795, 1976.
10. Ogawa K, Harata Y, Ichihara T, Kubo A, Hashimoto S. A practical method for position-dependent computer-scatter correction in single photon emission CT. *IEEE Trans Med Imag* 10: 408–412, 1991.
11. Kropp J, Ambrose KR, Knapp Jr FF, Nissen HP, Biersack HJ. Incorporation of iodinated IPPA and BMIPP fatty acid analogues into complex lipids from isolated rat heart. *Nucl Med Biol* 19: 283–288, 1992.
12. Takeishi Y, Chiba J, Abe S, Tonooka I, Komatani A, Tomoike H. Heterogeneous myocardial distribution of iodine-123 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) in patients with hypertrophic cardiomyopathy. *Eur J Nucl Med* 19: 775–782, 1992.
13. Nishimura T, Uehara T, Shimonagata T, Nagata S, Haze K. Clinical results with β-methyl-p-(^{123}I)iodophenylpentadecanoic acid, single-photon emission computed tomography in cardiac disease. *J Nucl Cardiol* 1: S65–S71, 1994.
14. Kawamoto M, Tamaki N, Yonekura Y, Magata Y, Tadamura E, Nohara R, et al. Significance of myocardial uptake of iodine 123-labeled beta-methyl iodophenyl pentadecanoic acid: Comparison with kinetics of carbon 11-labeled palmitate in positron emission tomography. *J Nucl Cardiol* 1: 522–528, 1994
15. Ohtsuki K, Sugihara H, Umamoto I, Nakamura Y, Nakagawa T, Nakagawa M. Clinical evaluation of hypertrophic cardiomyopathy by myocardial scintigraphy using ^{123}I-labelled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (^{123}I-BMIPP). *Nucl Med Commun* 15: 441–447, 1994.
16. Nishimura T. Approaches to identify and characterize hypertrophic myocardium. *J Nucl Med* 34: 1013–1019, 1993.
17. Chen SL, Uehara T, Morozumi T, Yamagami H, Kusuoka H, Nishimura T. Myocardial metabolism of ^{123}I-BMIPP in patients with hypertrophic cardiomyopathy. *Nucl Med Commun* 16: 336–343, 1995.
18. Taki J, Nakajima K, Bungo H, Shimizu M, Taniguchi M, Hisada K. ^{123}I-labelled BMIPP fatty acid myocardial scintigraphy in patients with hypertrophic cardiomyopathy: SPECT comparison with stress ^{201}Tl. *Nucl Med Commun* 14: 181–188, 1993.
19. Shimonagata T, Nishimura T, Uehara T, Hayashida K, Kumita S, Ohno A, et al. Discrepancies between myocardial perfusion and free acid metabolism in patients with hypertrophic cardiomyopathy. *Nucl Med Commun* 14: 1005–1013, 1993.
20. Wolfe CL, Keneddy PL, Kulkarni PV, Jansen DE, Gabliani GI, Corbett JR. Iodine-123 Phenylpentadecanoic acid myocardial scintigraphy in patients with left ventricular hypertrophy: Alterations in left ventricular distribution and utilization. *Am Heart J* 119: 1338–1347, 1990.
21. Kondo M, Kubo A, Yamazaki H, Ohsuzu F, Handa S, Tsugu T, et al. Thallium-201 myocardial imaging for evaluation of right-ventricular overloading. *J Nucl Med* 19: 1197–1203, 1978.
22. Ohsuzu F, Handa S, Kondo M, Yamazaki H, Tugo T, Kubo A, et al. Thallium-201 myocardial imaging to evaluate right ventricular overloading. *Circulation* 61: 620–625, 1980.
23. Weitzenblum E, Moyses B, Dickele MC, Methlin G. Detection of right ventricular pressure overloading by thallium-201 myocardial scintigraphy. *Chest* 85: 164–169, 1984.
24. Berger HJ, Matthay RA, Loke J, Marshall RC, Gottschalk A, Zaret BL. Assessment of cardiac performance with quantitative radionuclide angiocardiography: Right ventricular ejection fraction with reference to findings in chronic obstructive pulmonary disease. *Am J Cardiol* 41: 897–905, 1978.
25. Brent BN, Berger HJ, Matthay RA, Mahler D, Pytric L, Zaret BL. Physiologic correlates of right ventricular ejection fraction in chronic obstructive pulmonary disease: A combined radionuclide and hemodynamic study. *Am J Cardiol* 50: 255–262, 1982.
26. Brent BN, Mahler D, Matthay RA, Berger HJ, Zaret BL. Noninvasive diagnosis of pulmonary arterial hypertension in chronic obstructive pulmonary disease: Right ventricular ejection fraction at rest. *Am J Cardiol* 53: 1349–1353, 1984.
27. Marmor A, Blello DR, Sampathkumaran KS, Geltman EM, Slegel BA, Roberts R. A new scintigraphic technique for assessment of right atrial function. *Radiology* 139: 719–723, 1981.
28. Konstam MA, Kahn PC, Curran BH, Iodoine J, Wynne J, Holman BL. Equilibrium (Gated) radionuclide ejection fraction measurement in the pressure or volume overload right ventricle. *Chest* 85: 681–687, 1984.
29. Hayashida K, Nishimura T, Uehara T, Shimonagata T. Detection of right ventricular pressure overloading comparing of right ventricular uptake rate (RVUR) and right ventricular ejection fraction (RVEF). *KAKU IGAKU (Jpn J Nucl Med)* 23: 237–242, 1986.
30. Brooks H, Kirk ES, Vokonas PS, Urschel CW, Sonnenblick EH. Performance of the right ventricle under stress: Relation to right coronary flow. *J Clin Invest* 50: 2176–2183, 1971.
31. Vlahakes GJ, Turley K, Hoffman JIE. The pathophysiology of failure in acute right ventricular hypertension: Hemodynamic and biochemical correlations. *Circulation* 63: 87–95, 1981.
32. Gold FL, Bache RJ. Transmural right ventricular blood flow during acute pulmonary hypertension in the sedated dog. *Circ Res* 51: 196–204, 1982.
33. Manohar M, Transquilli WJ, Parks CM, Benson J, Theodorakis MC, Thurmon JC. Regional myocardial blood flow and coronary vasodilator reserve during acute right ventricular failure due to pressure overload in swine. *J Surg Res* 31: 382–391, 1981.
34. Schulman DS, Lazar JM, Ziady G, Grandis DJ, Flores AR, Orie JE. Right ventricular thallium-201 kinetics in pulmonary hypertension: Relation to right ventricular size and function. *J Nucl Med* 34: 1695–1700, 1993.