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Prediction of Cardiac Death in Hemodialysis Patients by Myocardial Fatty Acid Imaging

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Objectives The aim was to evaluate the potential of single-photon emission computed tomography (SPECT) to predict cardiac death in chronic hemodialysis patients using the iodinated fatty acid analogue iodine-123 (^{123}I)–β-methyl iodophenyl-pentadecanoic acid (BMIPP).

Background We previously reported that BMIPP SPECT could detect asymptomatic coronary artery disease with high sensitivity in hemodialysis patients.

Methods We prospectively enrolled 375 asymptomatic hemodialysis patients who had undergone dual SPECT using ^{123}I–BMIPP and ^{201}thallium (Tl) chloride. Patients who had a clinical history of myocardial infarction and/or coronary revascularization were excluded from the study. Uptake on SPECT images was graded in 17 segments on a 5-point scale (0 normal, 4 absent) and assessed as summed BMIPP or Tl scores.

Results During a 3.6 ± 1.0-year follow-up, 57 patients who had undergone coronary revascularization within 60 days of SPECT were excluded from the analysis. Among the remaining 318 patients (male/female: 170/148; 64 ± 12 years of age), 50 died of cardiac events (acute myocardial infarction 22, congestive heart failure 17, cardiac sudden death 11). Stepwise Cox hazard analysis associated cardiac death with age (≥70 years) and with severely abnormal BMIPP SPECT images (BMIPP summed scores ≥12: hazard ratio 21.894; $p < 0.0001$). Kaplan-Meier analysis showed that the cardiac death-free survival rates at 3 years were 61% and 98% in patients with BMIPP summed scores of ≥12 and <12, respectively.

Conclusions Severely impaired myocardial fatty acid metabolism, which might mainly reflect repetitive myocardial ischemia, can identify a high-risk group of cardiac death among hemodialysis patients. (J Am Coll Cardiol 2008;51: 139–45) © 2008 by the American College of Cardiology Foundation

Although maintenance dialysis prevents death from uremia, patient survival remains an important issue. Cardiovascular disease accounts for about 50% of reported deaths among patients undergoing maintenance hemodialysis in the U.S. (1). Even in Japan, cardiac death presently accounts for about 36.1% of the total number of deaths among dialysis patients (congestive heart failure [CHF] 25.8%, acute myocardial infarction [MI] 5.1%, cardiac sudden death 5.2%) (2). Compared with the general population, dialysis patients have a 10- to 20-fold greater incidence of cardiovascular death (3), which is probably due to the high prevalence of either underlying coronary artery disease before starting hemodialysis or cardiovascular risk factors in those with end-stage renal disease (ESRD) (4). The HEMO (Hemodialysis) study (5), which was a randomized multicenter investigation of 1,846 hemodialysis patients, showed that 80% of such patients had cardiovascular diseases at baseline, including ischemic heart disease (39%), CHF (40%), and arrhythmia (31%).

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Over 70% of the energy expended by the normal myocardium under aerobic conditions is derived from free fatty acid metabolism. Under hypoxic or ischemic conditions, the metabolism of fatty acids is suppressed and replaced with that of glucose, which consumes less oxygen but is also less efficient in terms of adenosine triphophosphate (ATP) synthesis. Re-

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Abbreviations and Acronyms

ATP = adenosine triphosphate
BMIPP = β-methyl iodophenyl-pentadecanoic acid
CABG = coronary artery bypass graft
CHF = congestive heart failure
CRP = C-reactive protein
ESRD = end-stage renal disease
^{123}I = ^{123}iodine
LV = left ventricular
MI = myocardial infarction
PCI = percutaneous coronary artery intervention
ROC = receiver-operating characteristic
SPECT = single-photon emission computed tomography
Tl = thallium

sistance to β-oxidation in mitochondria characterizes the branched free fatty acid analogue ^{123}I (^{123}iodine)–β-methyl iodophenyl-pentadecanoic acid (BMIPP). Therefore, single-photon emission computed tomography (SPECT) using ^{123}I–BMIPP as a tracer is considered to reflect fatty acid metabolism in the heart, and ischemic lesions due to coronary stenosis or spasm can be identified (6,7). Our previous findings indicated that BMIPP SPECT could detect asymptomatic coronary artery disease among hemodialysis patients (8). The accumulation of BMIPP in the heart correlates with a decrease in myocardial ATP content (9, 10), which is also closely associated with left ventricular (LV) wall motion (11). Thus, reduced intensity on BMIPP SPECT images might not only indicate coronary stenosis or spasm, but also reflect a myocardial energy-deficient state that is likely to cause serious cardiac events. The present study evaluates whether BMIPP SPECT can predict cardiac death in patients undergoing maintenance hemodialysis.

Patients and Methods

Patients. Entry and exclusion criteria for the study are summarized in Figure 1. Of 714 patients undergoing maintenance hemodialysis in Toujinkai Hospital, 646 fit the criteria for SPECT. However, 176 of those patients refused a SPECT examination. Therefore, we performed dual BMIPP and Tl SPECT on the remaining 470 hemodialysis patients between November 1, 2000, and October 31, 2002. Of these, 95 with apparent heart disease, including a history of myocardial infarction (MI), pulmonary disease, malignancy, or a history of coronary revascularization, such as coronary artery bypass graft (CABG) or percutaneous coronary artery intervention (PCI), at the time of SPECT were excluded from the study. The criteria for diagnosing old MI were a history of acute MI, abnormal Q waves in electrocardiograms, or abnormal wall motion and diminished LV wall thickness. Consequently, 375 hemodialysis patients without chest symptoms (male/female: 198/177; 65 ± 12 years of age) were enrolled in the study and followed up through October 31, 2005, until the end point was reached.

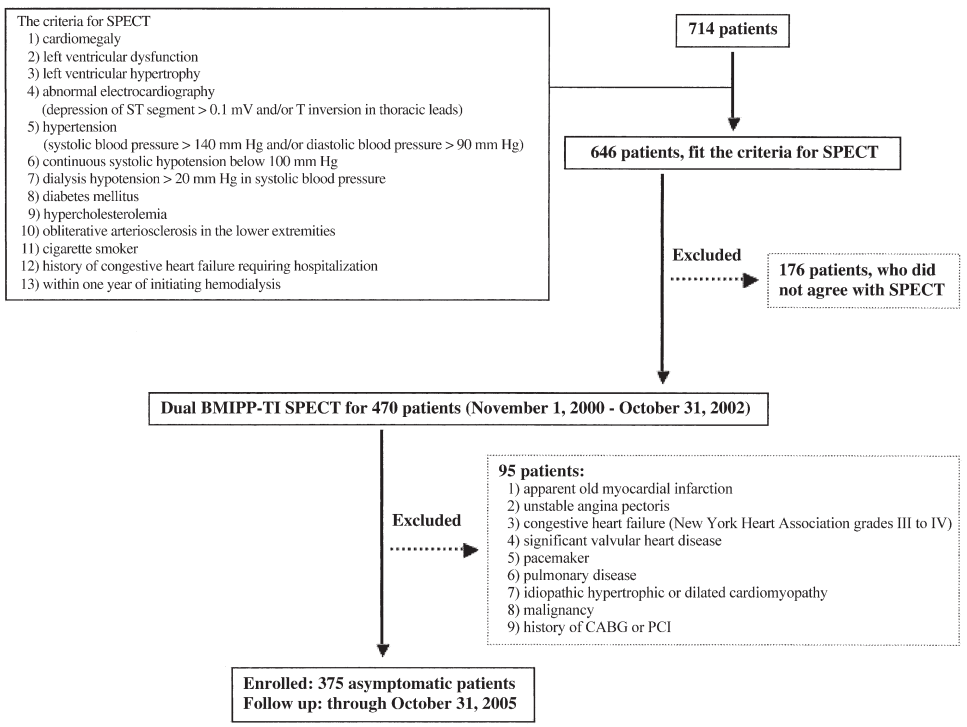

Figure 1 Entry and Exclusion of Study Participants

BMIPP = β-methyl iodophenyl-pentadecanoic acid; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; SPECT = single-photon emission computed tomography; Tl = thallium.

Histories of smoking and alcohol consumption were determined from a questionnaire. A smoking habit was defined as ≥10 cigarettes/week. Alcohol consumption was defined as alcohol intake of ≥20 g/week. The Ethics Committee for Human Research of Toujinkai Hospital approved this study, and all patients provided written informed consent to all procedures associated with the study before participation.

Radionuclide imaging. All patients underwent resting ^{123}I–BMIPP and ^{201}Tl dual myocardial scintigraphy after fasting for over 6 h on a midweek nondialysis day. Seated patients were injected intravenously with 111 MBq ^{123}I–BMIPP (Nihon Medi-Physics, Tokyo, Japan) and 111 MBq ^{201}Tl (Nihon Medi-Physics), and then ventricular SPECT images were acquired as described previously (8). Although cross-talk was not corrected, the results were validated using a myocardium phantom, ^{123}I, and ^{201}Tl. We confirmed that visual evaluation using the dual isotope protocol with ^{123}I and ^{201}Tl was not associated with any problems. The images were divided into 17 segments for semiquantitative analysis according to the standard myocardial segmentation for tomographic heart imaging established by the American Heart Association (12). The radioactivity of each segment was visually graded and assigned a score from 0 to 4 (0 = normal; 1 = mildly reduced; 2 = moderately reduced; 3 = severely reduced; and 4 = no uptake). The BMIPP and Tl SPECT scores for 17 myocardial segments were designated as summed BMIPP and Tl scores, respectively. A BMIPP–Tl mismatch score was defined as a difference between the summed BMIPP and Tl scores. The same experienced technician performed all scintigraphic procedures. All BMIPP and Tl SPECT images were interpreted within 1 week of the SPECT examination by the same 2 investigators, who were completely blinded to the clinical and laboratory information of the patients.

Echocardiography. The patients underwent 2-dimensionally guided M-mode echocardiography using a single ultrasonographic recorder (UF-8800, Fukuda Denshi, Tokyo, Japan) on a midweek nondialysis day of the week after SPECT, as previously described (8).

Biochemical and hematologic determinations. Blood samples (5 ml) were collected before initiating the midweek hemodialysis sessions and before the SPECT examination. Blood hemoglobin concentration, hematocrit, and serum concentrations of calcium, inorganic phosphorus, or high-sensitivity C-reactive protein were determined as the means of 4 measurements within 2 months before the SPECT examination. Serum concentrations of albumin or total cholesterol were determined as the means of 4 measurements within 4 months before the SPECT examination. The serum intact parathyroid hormone concentration was determined within 2 months, and plasma concentration of B-type natriuretic peptide was measured within 1 month of the SPECT examination.

End point. All 375 patients were followed up after SPECT at Toujinkai Hospital. The end point was cardiac-derived death, namely, cardiac sudden death and death due to acute MI or congestive heart failure (CHF). Cardiac sudden death was defined as death within 24 h of the time that the victim was last seen alive in a normal state of health, and cardiac diseases such as arrhythmias or acute coronary syndrome were considered to be the most frequent causes of death. Acute MI was diagnosed when new abnormal Q waves appeared on the electrocardiogram together with anterior chest pain or discomfort, when abnormal LV wall motion was recognized by echocardiography, and when serum concentrations of troponin-T and creatine phosphokinase-MB fraction were significantly elevated. Cardiologists in Toujinkai Hospital or Kyoto Second Red Cross Hospital diagnosed cardiac-derived death, and they did not know about SPECT images at the time of diagnosis.

Statistical analysis. Values are expressed as mean ± SD. We compared the means of continuous variables using a *t* test, and categoric data were analyzed using the chi-square test. Receiver-operating characteristic (ROC) analysis was performed to define thresholds for continuous variables. This analysis provided optimal sensitivity and specificity in predicting cardiac death. Thresholds were obtained from minimal false-positive and false-negative results, i.e., by minimizing the expression $(1 - \text{specificity})^2 + (1 - \text{sensitivity})^2$. We used Kaplan-Meier analysis and the log rank test to analyze survival. Multivariate analysis for prognosis was assessed using the Cox proportional hazard model. The number of events that occurred limited the number of variables included in this multivariate model. A p value of <0.05 was considered to be significant. Individuals without knowledge of the SPECT findings or the patients' profiles performed all statistical analyses.

Results

During follow-up, PCI and CABG were performed in 49 and 8, respectively, of 375 hemodialysis patients to treat asymptomatic coronary artery diseases detected by BMIPP SPECT. Data from these 57 patients were not included in the prognostic portion of the analysis, because coronary revascularization proceeded within 60 days of the SPECT examination (13). The resulting study cohort comprised the remaining 318 ESRD patients undergoing maintenance hemodialysis for a mean of 98.5 ± 95.8 months (male/female: 170/148; mean age 64 ± 12 years of age). The mean duration of follow-up after the SPECT examination was 3.6 ± 1.0 years. The etiology of renal failure involved chronic glomerular disease in 58.5% (186 of 318), diabetes mellitus in 32.7% (104 of 318), polycystic kidney disease in 4.1% (13 of 318), nephropathy due to collagen diseases in 1.6% (5 of 318), nephrosclerosis in 1.3% (4 of 318), urolithiasis in 0.6% (2 of 318), gouty kidney in 0.6% (2 of 318), and streptomycin-induced nephropathy in 0.6% (2 of 318) of the patients. Of the 318 patients studied, 75 underwent coronary angiography at the Department of Interventional Cardiology of the Kyoto Second Red Cross

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Table 1 Clinical Characteristics of Hemodialysis Patients With or Without Cardiac Death

	Cardiac Death (n = 50)	No Cardiac Death (n = 268)	p Value
Age (yrs)	72.3 ± 11.0	62.0 ± 11.4	<0.001
Male gender, n (%)	32 (64.0%)	138 (51.5%)	0.141
Dialysis duration (months)	83.1 ± 102.5	101.3 ± 94.4	0.216
Body mass index (kg/m^2)	16.6 ± 4.1	19.1 ± 4.2	<0.001
Diabetes mellitus, n (%)	19 (38.00%)	85 (31.72%)	0.481
Systolic blood pressure before dialysis (mm Hg)	144.1 ± 19.6	143.9 ± 16.3	0.920
Diastolic blood pressure before dialysis (mm Hg)	71.3 ± 11.8	77.2 ± 11.0	<0.001
LV internal end-diastolic dimension (mm)	50.4 ± 9.1	48.9 ± 7.3	0.204
LV internal end-systolic dimension (mm)	35.0 ± 10.2	30.4 ± 7.2	<0.001
LV ejection fraction (%)	56.6 ± 16.4	67.3 ± 12.0	<0.001
LV mass index (g/m^2)	147.4 ± 51.3	127.0 ± 51.2	0.010
Serum albumin (g/l)	36.8 ± 3.8	38.7 ± 3.9	0.001
Serum total cholesterol (mmol/l)	4.33 ± 0.90	4.39 ± 1.00	0.675
Serum calcium (mmol/l)	2.34 ± 0.20	2.26 ± 0.19	0.011
Serum inorganic phosphorus (mmol/l)	1.64 ± 0.43	1.73 ± 0.36	0.095
Serum intact parathyroid hormone (pg/ml, log)	2.17 ± 0.41	2.22 ± 0.41	0.414
Serum hsCRP (mg/l)	3.6 ± 2.8	4.1 ± 3.0	0.216
Plasma B-type natriuretic peptide (pg/ml, log)	2.45 ± 0.48	2.41 ± 0.33	0.517
BMIPP summed score	20.4 ± 10.6	6.0 ± 8.1	<0.001
Tl summed score	6.5 ± 3.8	3.0 ± 4.3	<0.001

BMIPP = β-methyl iodophenyl-pentadecanoic acid; hsCRP = high-sensitivity C-reactive protein; LV = left ventricular; Tl = thallium.

Hospital within 60 days of the BMIPP SPECT, but none received coronary revascularization such as PCI or CABG, although some had significant coronary stenotic lesions.

Cardiac events and baseline characteristics. Of the 318 study participants, 50 (15.7%) died of cardiac events (acute MI 22, CHF 17, and cardiac sudden death 11) during a mean follow-up period of 3.6 ± 1.0 years. After the onset of acute MI, 13 patients died without coronary revascularization and 9 patients received emergency coronary angiography and ad hoc PCI, but cardiac death resulted within 24 h after PCI. Acute MI was not the cause of death among all 17 patients who died of CHF. The mean values of patients who died of cardiac events compared with those who did not revealed that they were older and that LV end-systolic dimension, LV mass index, and serum calcium concentration, as well as summed BMIPP or Tl scores, were higher, whereas body mass index, diastolic blood pressure before dialysis, LV ejection fraction, and serum albumin concentrations were lower (Table 1). We found no differences between patients with and without cardiac death in terms of the mean values of dialysis duration, systolic blood pressure before or after dialysis, diastolic blood pressure after dialysis, LV end-diastolic dimension, hematocrit, blood hemoglobin concentration, serum concentrations of inorganic phosphorus, total cholesterol, intact parathyroid hormone, high-sensitivity C-reactive protein concentration, plasma B-type natriuretic peptide concentration, and ratios of male gender, diabetes mellitus, smoking habit, alcohol consumption, or prescribed medications such as calcium-channel blockers, angiotensin I-converting enzyme inhibitors, angiotensin II type-1 receptor blockers, alpha$_1$-blockers, beta-blockers, nitrates, antiplatelet drugs, anticoagulants, and statins.

Association between baseline characteristics and subsequent cardiac events. We performed ROC analysis of 8 parameters that significantly differed ($p < 0.001$) between patients who died of cardiac death and those who did not. Table 2 shows the cutoff values used to predict cardiac death, the area under the curve obtained by ROC analysis, and the sensitivity and specificity for cardiac death regarding these cutoff values. Stepwise Cox hazard analysis of the 5 highest-ranking parameters in the ROC analysis (BMIPP summed score, Tl summed score, age, LV ejection fraction, and body mass index) showed that cardiac death was significantly associated with age of ≥70 years (hazard ratio 2.358) and particularly with highly abnormal BMIPP SPECT findings (BMIPP score of ≥12: hazard ratio 21.894) (Table 3). Kaplan-Meier survival estimates revealed

Table 2 Cutoff Values for Predicting Cardiac Death Obtained by ROC Analysis

	Cutoff Values	AUC	Sensitivity	Specificity
BMIPP summed score	≥12	0.894	90%	80%
Tl summed score	≥3	0.758	84%	63%
Age (yrs)	≥70	0.742	64%	75%
LV ejection fraction (%)	<60	0.704	52%	82%
Body mass index (kg/m^2)	<18.5	0.670	72%	53%
Diastolic blood pressure before dialysis (mm Hg)	<75	0.659	70%	61%
LV internal end-systolic dimension (mm)	≥34	0.648	56%	76%
Serum albumin concentration (g/l)	<39	0.643	68%	55%

AUC = area under the curve; ROC = receiver-operating characteristic; other abbreviations as in Table 1.

Table 3 Multivariate Analysis of Clinical Factors Predicting Cardiac Death in Hemodialysis Patients Using Stepwise Cox Hazard Model

	Hazard Ratio	95% CI	p Value
Age (≥70 yrs)	2.358	1.308–4.248	0.004
BMIPP summed score (≥12)	21.894	8.542–56.114	<0.0001

BMIPP = β-methyl iodophenyl-pentadecanoic acid; CI = confidence interval.

that the event-free rates of cardiac death at 3 years were 61% in patients with summed BMIPP score of ≥12 and 98% in patients with a summed BMIPP score <12 (Fig. 2A). Furthermore, as the BMIPP summed scores increased, event-free rates of cardiac death worsened when the patients were divided into 5 subgroups according to their summed BMIPP scores (Fig. 2B). Figure 3 shows dual BMIPP and Tl SPECT images from patients who died of acute MI, CHF, and sudden cardiac death.

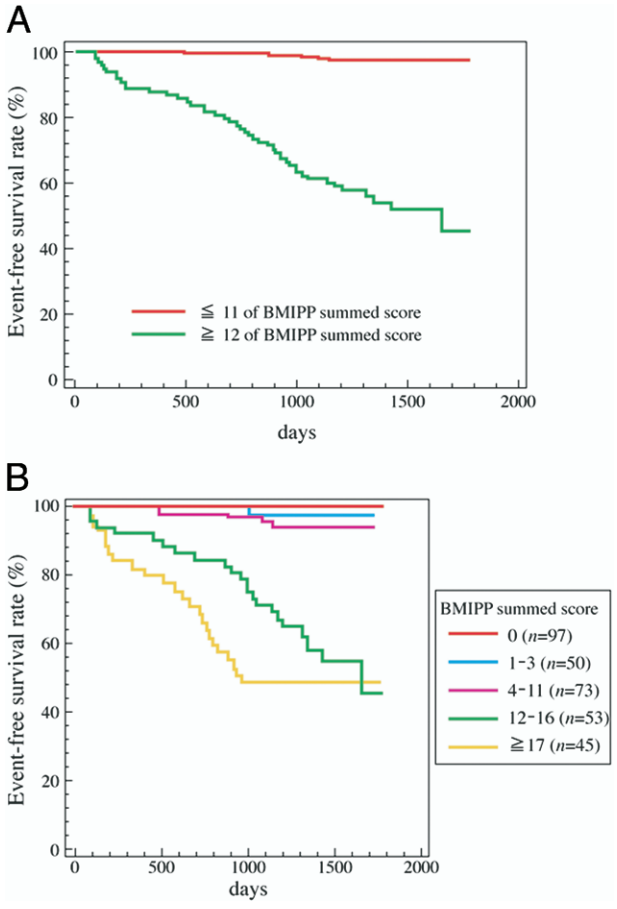

Figure 2 Kaplan-Meier Analysis of Cardiac Death-Free Survival Rate by BMIPP SPECT

(A) Event-free survival rates of cardiac death at 3 years are 61% for patients with BMIPP summed scores of ≥12 and 98% for those with scores <12. Log rank test: $p < 0.0001$. **(B)** Event-free rates of cardiac death became aggravated with increasing summed BMIPP scores when separated into 5 subgroups according to BMIPP summed scores. Log rank test: $p < 0.0001$. Abbreviations as in Figure 1.

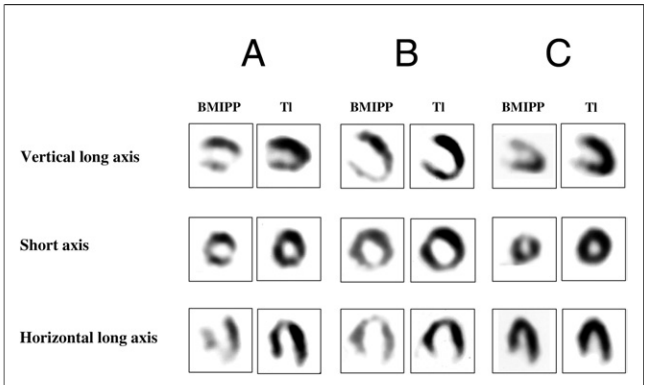

Figure 3 BMIPP and Tl SPECT Images From Patients Who Died of Cardiac Events

(A) A 75-year-old woman, whose summed BMIPP and Tl scores were 37 and 7, respectively, died of acute myocardial infarction 11 months after SPECT. Coronary angiography within 60 days of BMIPP SPECT revealed significant stenoses in the left main trunk (75%) right coronary artery (#2 75%), left anterior descending artery (#6 75%, #9 90%), and left circumflex artery (#12 75%, #13 75%). The patient refused invasive therapy, thus negating the possibility of coronary intervention. **(B)** A 74-year-old man whose summed BMIPP and Tl scores were 36 and 6, respectively, died of congestive heart failure 31 months after SPECT. Coronary angiography did not find significant stenosis of >50% within 60 days of SPECT. **(C)** A 61-year-old man whose summed BMIPP and Tl scores were 18 and 0, respectively, died of sudden cardiac events 38 months after SPECT. Coronary angiography did not find significant stenosis within 60 days of SPECT. Abbreviations as in Figure 1.

BMIPP–Tl mismatch. The mean BMIPP–Tl mismatch score was higher in patients with cardiac death than in those without (14.0 ± 8.1 [n = 50] vs. 2.9 ± 4.6 [n = 268]; $p < 0.001$). When the cutoff value of BMIPP–Tl mismatch score was determined to be 7 by ROC analysis, the sensitivity and specificity of BMIPP–Tl mismatch for predicting cardiac death were 86% and 88%, respectively. Kaplan-Meier survival estimates revealed that the event-free rates of cardiac death at 3 years were 53% in patients with BMIPP–Tl mismatch of ≥7 and 96% in patients with BMIPP–Tl mismatch <7 (Fig. 4).

Discussion

Of 318 ESRD patients on maintenance hemodialysis, 50 died of cardiac-related causes during a 3.6 ± 1.0-year follow-up. Stepwise Cox hazard analysis showed that cardiac death was significantly associated with advanced age and, particularly, with severely abnormal BMIPP SPECT findings. Kaplan-Meier survival estimates revealed that event-free rates of cardiac death worsened as the summed BMIPP score increased. A BMIPP–Tl mismatch, which indicates myocardial ischemia, was also associated with cardiac death. Highly impaired myocardial fatty acid metabolism evaluated by BMIPP SPECT, which might mainly reflect silent myocardial ischemia from an undefined mechanism (8), can identify a group at high risk for cardiac death among asymptomatic hemodialysis patients.

The main cause of cardiac death in the HEMO study (5) was ischemic heart disease, which was associated not only

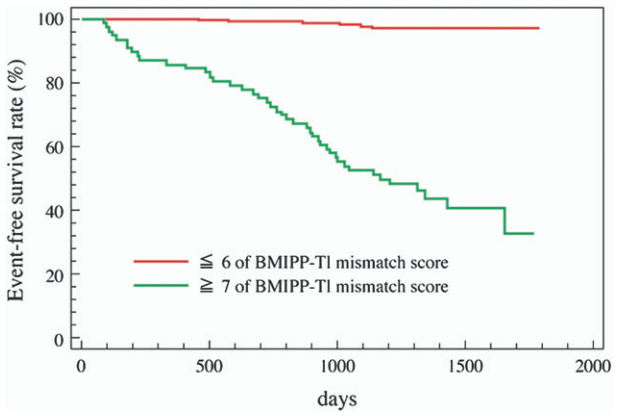

Figure 4 **Kaplan-Meier Analysis of Cardiac Death-Free Survival Rate by BMIPP–Tl Mismatch**

Event-free survival rates of cardiac death at 3 years are 53% for patients with mismatch scores of ≥7 and 96% for those with scores <7. Log rank test: $p < 0.0001$. Abbreviations as in Figures 1 and 3.

with deaths due to myocardial ischemia (relative risk 2.82) but also with those associated with CHF (relative risk 1.71) and arrhythmia (relative risk 1.20). Intramyocardial arteriolar wall thickening and reduced capillary density in the myocardium have been identified in animal models of renal failure and in uremic patients (14–16). Interstitial fibrosis in the myocardium is more severe in patients with ESRD than with primary hypertension and diabetes mellitus (16). All of these myocardial abnormalities in hemodialysis patients cause microcirculatory disturbances and render the myocardium more susceptible to ischemic injury. Therefore, coronary artery stenosis or spasm is thought to exacerbate myocardial ischemia more in patients with than without ESRD.

A BMIPP–Tl mismatch was also associated with cardiac death among hemodialysis patients. The area with a BMIPP–Tl mismatch was a histologic mixture of myocardium and fibrous tissue that was identified only in ischemic myocardium when the extent of fibrotic changes was <20% (17). Positron emission tomography has demonstrated that areas with a mismatch have high levels of ^{18}F-fluorodeoxyglucose (18). Because patients with a history of MI were excluded from the present study, mismatch between BMIPP and Tl detected in asymptomatic hemodialysis patients is thought to indicate myocardial ischemia (19, 20). This finding supports the notion that myocardial ischemia is involved in cardiac death among this population.

Impaired myocardial fatty acid metabolism also seems to be involved in the development of ventricular arrhythmias. Mori et al., using BMIPP SPECT, found that ventricular arrhythmias are closely associated with abnormal myocardial fatty acid metabolism (21). Mitochondrial ATP-sensitive K^+ channels that are activated by a reduction in ATP might help to protect the myocardium against ischemia-induced arrhythmias (22), but activation of these channels seems to be attenuated in renal failure (23).

Stress Tl SPECT with exercise and/or vasodilative drugs such as dipyridamole or ATP can be useful for predicting cardiovascular events in dialysis patients (24–26). On the other hand, the predictive value of BMIPP SPECT for major cardiac events in patients with acute MI treated with PCI (27) and with known or suspected coronary artery disease (28), without ESRD, has been reported. Because the prognostic value of BMIPP SPECT for cardiac events is reportedly similar to that of stress Tl SPECT in non-ESRD patients (29), this procedure should be a useful modality for predicting cardiac events in ESRD patients without exercise or drug administration.

Study limitations. The mean age of the study participants was relatively high at 64 years. Advanced age is generally an independent risk factor for cardiac death, and age was significantly associated with cardiac death in the present study. We considered 11 sudden deaths to be cardiac death, although a coronary origin was not clearly determined. We could not completely eliminate the possibility that those deaths were due to hyperkalemia or some other cause. From the viewpoint of statistical analysis, the variable selection procedure for the multivariate model is not likely to be specified a priori and might be unable to detect other significant variables in the univariate analysis that have less significance. Finally, because the study was relatively small, the predictive value of BMIPP SPECT could not be defined. A larger patient population is needed to establish the clinical implications and prognostic value of this method.

Conclusions

We previously showed that BMIPP SPECT could detect asymptomatic coronary artery disease with high sensitivity in patients on hemodialysis (8). In the present prospective cohort study, we revealed that significantly impaired myocardial fatty acid metabolism detected by BMIPP SPECT might predict the occurrence of cardiac death in asymptomatic hemodialysis patients. Since patients with a history of MI were not included in the present study, highly abnormal BMIPP SPECT findings are thought to mainly indicate myocardial ischemia. Undergoing coronary angiography to diagnose myocardial ischemia such as coronary artery stenosis, spasm, or microcirculatory disturbance in patients with highly abnormal BMIPP SPECT findings and then treating it by coronary revascularization or medication should improve the survival of hemodialysis patients. Thus, BMIPP SPECT might be a new modality with which to identify a group of patients on chronic hemodialysis at high risk of cardiac death without adding stress.

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