

1 **Original article**

2 **The Utility of a Combination of ^{99m}Tc-MIBI Washout Imaging and Cardiac Magnetic**
3 **Resonance Imaging in the Evaluation of Cardiomyopathy**

4

5 Running head: Imaging of cardiomyopathy.

6

7 Moriaki Yamanaka, MD¹), Shoichiro Takao, MD, PhD²), Hideki Otsuka, MD, PhD³), Yoichi
8 Otomi, MD, PhD¹), Saho Irahara, MD¹), Yamato Kunikane, RT⁴), Satoru Takashi, RT⁴), Airi
9 Yamamoto, RT⁵), Masataka Sata MD, PhD⁶), Masafumi Harada, MD, PhD¹)

10 ¹)Department of Radiology, Tokushima University Hospital.

11 ²)Department of Diagnostic Radiology, Graduate School of Biomedical Sciences, Tokushima
12 University.

13 ³)Department of Medical Imaging/Nuclear Medicine, Graduate School of Biomedical Sciences,
14 Tokushima University.

15 ⁴)Division of Clinical Technology, Tokushima University Hospital.

16 ⁵)Department of Radiology, Takamatsu Municipal Hospital.

17 ⁶)Department of Cardiovascular Medicine, Graduate School of Biomedical Sciences,
18 Tokushima University.

19

20 Funding:

21 None

22 Total word count: 4467 words

23

24 Corresponding author

25 Shoichiro Takao, MD, PhD

26 Department of Diagnostic Radiology, Graduate School of Biomedical Sciences, Tokushima

27 University, 3-18-15 Kuramoto-Cho, Tokushima 770-8509, Japan

28 E-mail: takao@tokushima-u.ac.jp, Tel: +81-88-633-9865, Fax: +81-88-633-7468

29

30 Author

31 Moriaki Yamanaka, MD

32 Department of Radiology, Tokushima University Hospital, 2-50-1 Kuramoto-Cho, Tokushima

33 770-8503, Japan

34 E-mail: yamanaka_tokudai@yahoo.co.jp, Tel: +81-88-633-7173, Fax: +81-88-633-7174

35 The type of article: Original Article

36

37 **Abstract**

38 *Background:* In cardiomyopathy, ^{99m}Tc -MIBI washout can reflect mitochondrial dysfunction
39 and late gadolinium enhancement (LGE) on cardiac magnetic imaging (MRI) is associated with
40 tissue fibrosis. We sought to determine the relationship between ^{99m}Tc -MIBI uptake, ^{99m}Tc -
41 MIBI washout, and LGE on MRI in patients with cardiomyopathy.

42 *Methods:* Twenty-one patients underwent rest myocardial perfusion scintigraphy at 45 minutes
43 (early) and 4 hours (delayed) after intravenous ^{99m}Tc -MIBI administration and cardiac MRI.
44 We assessed myocardial perfusion, ^{99m}Tc -MIBI washout, and LGE. We divided the left
45 ventricle (LV) wall into 16 segments using a polar map. Then, we classified each segment into
46 5 groups according to ^{99m}Tc -MIBI uptake in early-rest images and washout. Additionally, we
47 created a contingency table based on LGE presence/absence in the groups.

48 *Results:* We evaluated 336 segments in 21 patients. ^{99m}Tc -MIBI uptake was decreased in 168
49 segments in the early-rest ^{99m}Tc -MIBI images. ^{99m}Tc -MIBI washout was observed in 108
50 segments with either normal perfusion or reduced perfusion in the early-rest ^{99m}Tc -MIBI
51 images. LGE was positive in 104 segments. A contingency table analysis with Fisher's exact
52 test showed that LGE was observed significantly more frequently in the segments with
53 decreased ^{99m}Tc -MIBI uptake ($p < 0.001$). In segments without a decreased ^{99m}Tc -MIBI uptake,
54 there was a significant correlation between increased ^{99m}Tc -MIBI washout and the presence of

55 LGE ($p = 0.033$).

56 *Conclusions:* In cardiomyopathy, the mitochondrial dysfunction in the early stage is shown as
57 ^{99m}Tc -MIBI washout, and fibrotic changes in the myocardium in advanced stages are shown as
58 LGE on cardiac MRI. The severity of myocardial damage and the clinical stage of
59 cardiomyopathy can be evaluated using multimodal imaging.

60

61 **Keywords:** cardiomyopathy, late gadolinium enhancement (LGE) ^{99m}Tc -MIBI, washout.

62

63

64

65

66 **Introduction**

67 Cardiomyopathy is associated with several kinds of myocardial injury. Radionuclide
68 studies and cardiac magnetic resonance imaging (MRI) can evaluate myocardial impairment
69 and cardiac function; they play important roles in cardiomyopathy diagnosis.

70 ^{99m}Tc-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) is a widely used perfusion radiotracer for
71 coronary artery disease detection. ^{99m}Tc-MIBI is taken up by passive diffusion as cations into
72 cardiomyocytes and subsequently into the negatively charged mitochondria (1). The
73 myocellular uptake and retention of MIBI are strongly dependent on the mitochondrial and
74 plasma membrane potentials, both qualitatively and quantitatively (1). In damaged
75 cardiomyocytes, the mitochondria's negative membrane potential becomes smaller, and the
76 potential difference with cations decreases. As a result, ^{99m}Tc-MIBI uptake is reduced, and
77 retention in the myocardium decreases. ^{99m}Tc-MIBI is then released outside of the myocardium,
78 and washout increases. Previous studies have shown that restriction of ^{99m}Tc-MIBI myocardial
79 uptake is associated with ongoing myocardial damage (2, 3). Additionally, the increase in
80 ^{99m}Tc-MIBI washout may suggest altered mitochondrial function or mitochondrial dysfunction
81 (4,5). However, the significance of evaluating ^{99m}Tc-MIBI washout for clinical diagnosis of
82 cardiomyopathy remains unclear.

83 Cardiac MRI is considered a gold standard modality for noninvasive myocardial function

84 assessment and can visualize and quantify scarring using late gadolinium enhancement (LGE)
85 (6). LGE regions are defined as necrotic or fibrotic regions caused by prolonged retention of
86 gadolinium, compared with normal regions.

87 Previous reports have shown that LGE is a useful and reproducible method for assessing
88 myocardial fibrosis in patients with cardiomyopathy (7–9). Furthermore, some reports have
89 revealed a relationship between a decrease in ^{99m}Tc -MIBI uptake and LGE (10, 11). However,
90 the relationship between ^{99m}Tc -MIBI washout and LGE in cardiomyopathy has not been well
91 characterized.

92 We hypothesized that ^{99m}Tc -MIBI washout, which is thought to reflect mitochondrial
93 dysfunction, may help assess earlier myocardial damage than LGE, which is thought to reflect
94 fibrosis. We investigated the relationship between the presence or absence of ^{99m}Tc -MIBI
95 uptake abnormality, increased ^{99m}Tc -MIBI washout, and LGE. Further, this study determined
96 whether the presence of ^{99m}Tc -MIBI washout was significantly associated with myocardial
97 fibrosis, as detected by MRI in patients with cardiomyopathy. Moreover, we sought to
98 determine the relationship between ^{99m}Tc -MIBI uptake, ^{99m}Tc -MIBI washout, and LGE on
99 cardiac MRI in patients with cardiomyopathy.

100

101

102 **Material and Methods**

103 **Study population**

104 We included 25 patients with cardiomyopathy who presented to us between January 2011
105 and November 2017. These patients showed early and delayed-rest myocardial perfusion
106 imaging (MPI) on ^{99m}Tc-MIBI (FUJI-Toyama RI Pharma, Tokyo, Japan) and gadolinium-
107 enhanced cardiac MRI. MRI was performed within an average of 13 days (range: 0–26 days)
108 using ^{99m}Tc-MIBI scintigraphy. All patients were >18 years and clinically diagnosed with
109 cardiomyopathy. No patient had received drugs for cardiomyopathy, such as steroids, before
110 the examination, and none had undergone any intervention, such as pacemaker implantation or
111 surgery before examination. All patients underwent coronary angiography. No patient showed
112 significant coronary stenosis. This study was approved by Tokushima University Hospital's
113 Institutional Review Board and Ethics Committee. The need for written informed consent was
114 waived.

115

116 **^{99m}Tc-MIBI protocol**

117 Rest imaging protocol was 45 minutes (early) and 4 hours (delayed) after intravenous
118 administration of 370–500 MBq of ^{99m}Tc-MIBI (2, 12). The patient was asked to ingest a
119 chocolate bar or milk before imaging to reduce artifacts associated with abdominal

120 accumulation. Data acquisition was performed using a dual-head gamma camera (E.CAM;
121 Toshiba Medical Corporation Systems, Odawara, Japan). For each image, electrocardiogram-
122 gated single-photon emission computed tomography (SPECT) was conducted following planar
123 imaging. The ^{99m}Tc-MIBI scan protocol and parameters included: in planar images: matrix size,
124 256×256; magnification, 1.00; collecting time, 3 minutes front, 3 minutes lateral; in SPECT
125 images: matrix size, 64×64; magnification, 1.78, step and shoot, non-circular orbit, 30 views;
126 collection time, 30 seconds per view; rotary angle, 180°; scan duration, 900 seconds;
127 reconstruction via the ordered subset expectation maximization method, and Gaussian filter.

128

129 ^{99m}Tc-MIBI data analyses

130 **Image Reconstruction**

131 The cardiac function analysis software program CardioBull (Fujifilm RI Pharma Co., Ltd.,
132 Tokyo, Japan) was used for the analysis of SPECT images. By importing the short-axis images
133 into the program, the optimal apical and basal slices were automatically determined. For
134 qualitative polar map creation, automatic co-registration was applied for pairs of short-axis
135 images (13). A myocardial perfusion polar map was generated using a circumferential profile
136 curve analysis with the apical radial sampling method (14). LV wall was divided into 17
137 segments (15) (Fig. 1a).

138 **Image interpretation**

139 A double-board-certified physician, H.O. (diagnostic radiology and nuclear medicine),
140 evaluated the ^{99m}Tc-MIBI images visually in this study. We applied a 5-point visual scale to
141 each segment (defect score: 0, normal uptake; 1, mildly decreased; 2, moderately decreased; 3,
142 severe decreased; 4, perfusion defect) in the early and delayed-rest images (2,12). We evaluated
143 the washout by scoring and judging the uptake in the early- and delayed-rest images and
144 comparing the two; we considered an increase of one or more segmental defect scores (2, 12).

145

146 **Segmental Classification**

147 We defined a defect score 0 as normal uptake and defect score 1-4 as abnormal uptake in
148 the early-rest images. The subjects were classified into the following five groups based on
149 ^{99m}Tc-MIBI uptake in the early-rest images and presence or absence of ^{99m}Tc-MIBI washout:
150 Group 1, normal uptake without ^{99m}Tc-MIBI washout; Group 2, normal uptake with washout;
151 Group 3, abnormal uptake without washout; Group 4, abnormal uptake with washout; Group
152 5, abnormal uptake and fill-in (Fig. 1b, e).

153

154 **Cardiac MRI**

155 Cardiac MRI was performed with a 1.5-T MRI scanner (GE Signa Excite 1.5 T; General

156 Electric, Milwaukee, WI, USA) using a phased-array coil. All cardiac MR images were
157 electrocardiographically gated and obtained during repeated breath-holds. To evaluate the left
158 ventricle's anatomy, short-axis images, and two-, three-, and four-chamber long-axis views
159 were obtained by cine-MRI, using a steady-state free-precession technique. Gadopentetate
160 meglumine (0.15 mmol/kg; Magnevist; Schering AG, Berlin, Germany) was then administered
161 at a rate of 3–4 mL/s using a power injector. LGE images were acquired 10 min after injection
162 of gadopentetate meglumine, with an inversion-recovery SSFP pulse sequence and inversion
163 time of 300 ms. Image parameters were as follows: repetition time (TR), 5.8 ms; excitation
164 time (TE), 2.3 ms; image matrix, 256×128; field of view, 360 mm; slice thickness, 10 mm;
165 spacing, 2–4 mm; flip angle, 12°; and k-space/cardiac cycle, 8–12 lines. Images were acquired
166 during short breath-holding (12–15 seconds) at end inspiration (16).

167

168 **Cardiac MRI data analyses**

169 We analyzed the LGE images using the Ziostation 2 software program (Ziosoft, Tokyo,
170 Japan). Short-axis LGE images were used for the analysis. We excluded the apex and base
171 segments as these sections' scans did not include the left ventricle muscle or the beveled
172 myocardium, which may have caused incorrect signal intensities. LGE regions were
173 automatically defined as those exhibiting a signal intensity above a predetermined threshold.

174 We used a threshold of five standard deviations (SD) above the signal intensity of the non-
175 damaged myocardium, as LGE quantification with this threshold showed the best agreement
176 with the visual assessment and the best reproducibility among different techniques thresholds
177 (17). The results were shown as a polar map divided into 16 segments. We excluded the apex
178 from the standard 17-segment model, as the apex cannot be assessed in short-axis LGE images.
179 The extent of LGE was calculated as the area ratio (%) for each segment. In this study, the
180 qualitative evaluation was performed as with the analysis of ^{99m}Tc-MIBI. Positive LGE was
181 defined as an extent of $\geq 60\%$ LGE in the segment. Negative LGE was defined as an extent
182 $< 60\%$ (Fig. 1c–e).

183

184 **Statistical analyses**

185 Continuous variables are expressed as mean \pm standard deviation. Categorical variables are
186 described as numbers and percentages. The Kolmogorov–Smirnov test was used to evaluate
187 the normality of the data distribution. The data of each segment were considered as independent
188 qualitative data, and their consistency was examined. Fisher’s exact test was used to examine
189 differences in proportion (categorical variables). These statistical analyses were performed
190 with IBM SPSS Statistics 23 software program for Windows (IBM Corp., Armonk, NY, USA).
191 Statistical significance was set at $p < 0.05$.

192

193 **Results**

194 **Patients' characteristics**

195 Among the 25 patients, four patients we excluded because of poor MRI image quality due
196 to motion artifacts. Therefore, only 21 patients were analyzed. Patient characteristics are shown
197 in Table 1. Patients' clinical diagnoses were classified as idiopathic or specific cardiomyopathy,
198 according to Japanese guidelines (18).

199

200 **Image Findings**

201 **^{99m}Tc-MIBI**

202 We evaluated 336 segments in 21 patients. The details of early-rest images defect scores
203 of 0, 1, 2, 3, and 4 were 168, 96, 42, 21, and 9 segments, respectively. In all 336 segments; an
204 increase in ^{99m}Tc-MIBI washout was observed in 108 segments. We classified the segments
205 into groups 1, 2, 3, 4, and 5 with 106, 62, 101, 46, and 21 segments, respectively.

206

207 **Cardiac MRI**

208 LGE regions were observed in 104 segments.

209

210

211 **Relationship between ^{99m}Tc-MIBI and cardiac MRI**

212 Table 2 shows the numbers of segments classified according to the presence or absence
213 of ^{99m}Tc-MIBI washout and LGE. No significant association was observed between the
214 presence or absence of ^{99m}Tc-MIBI washout and that of LGE (Fisher's exact test, p = 0.165).

215 Table 3 shows the numbers of segments classified according to the defect score in the
216 early-rest images and the presence or absence of LGE. LGE positive counts increased
217 significantly with increase in the defect score segments (Fisher's exact test, p < 0.001).

218 Groups 1 and 2 were classified as normal perfusion of ^{99m}Tc-MIBI. Among the 168
219 segments classified into groups 1 or 2, washout was observed in 62 segments (36.9%), and
220 LGE regions were observed in 29 segments (17.2%). LGE was significantly more frequent in
221 segments with ^{99m}Tc-MIBI washout than in those without (Fisher's exact test, p = 0.033). (Table
222 4).

223 Groups 3 and 4 were classified as having decreased ^{99m}Tc-MIBI uptake. Among the 147
224 segments classified into group 3 or 4, washout was observed in 23 segments (15.6%) and LGE
225 regions in 66 segments (44.8%). There was no significant association between the presence or
226 absence of ^{99m}Tc-MIBI washout and LGE frequency (Fisher's exact test, p = 0.475). (Table 5).

227

228

229 **Discussion**

230 In this study, we investigated the association of ^{99m}Tc -MIBI initial uptake, ^{99m}Tc -MIBI
231 washout, and LGE with MRI. LGE was more frequently observed in segments with decreased
232 ^{99m}Tc -MIBI uptake than those with normal uptake. Furthermore, in the segments without an
233 abnormal ^{99m}Tc -MIBI uptake in early-rest images, a significant association was observed
234 between increased ^{99m}Tc -MIBI washout and LGE presence.

235 In previous studies, researchers compared the diagnostic significance of the presence of
236 LGE on cardiac MRI with that of an abnormal pattern of perfusion/metabolism. Those studies
237 reported that the diagnostic ability of LGE is better for patients with moderate or more severe
238 myocardial fibrosis, whereas, for those with the early-stage disorder, evaluation of the
239 perfusion/metabolism mismatch is a more sensitive measurement (11, 19). The results of those
240 studies also indicated that compared with the presence of LGE, the presence of mismatches
241 correlates more closely with the survival rate in patients with cardiomyopathy, suggesting that
242 myocardial evaluation by ^{99m}Tc -MIBI is more sensitive than LGE.

243 Carvalho *et al.* have shown that approximately 90% of ^{99m}Tc -MIBI *in vivo* is associated
244 with mitochondria in an energy-dependent manner as a free cationic complex (20). Piwnicka-
245 Worms *et al.* reported that in the ischemic model, myocardial ^{99m}Tc -MIBI uptake was
246 significantly decreased in cases of mild ischemia and further decreased in cases of severe

247 ischemia (3). Thus, retention of ^{99m}Tc -MIBI in the myocardium is closely related to normal
248 mitochondrial function. Additionally, in the damaged myocardium, impairment in energy
249 production functions and transfer in mitochondria can result in the rapid release of ^{99m}Tc -MIBI
250 (1, 20).

251 Sekiguchi M *et al.*, in biopsy specimens from the left ventricle of patients with
252 hypertrophic cardiomyopathy, have shown that abnormal giant mitochondria resulted from
253 abnormal metabolic processes in the myocardium (21). Sarai *et al.* have reported that ^{99m}Tc -
254 MIBI washout correlates with mitochondrial dysfunction in cardiac sarcoidosis (22). Other
255 reports have shown mitochondrial dysfunction occurring in the impaired myocardium of
256 cardiomyopathies (23, 24). A recent report has shown that an increase in the ^{99m}Tc -MIBI
257 washout was correlated with decreased myocardial mitochondrial mRNA expression or an
258 abnormal mitochondrial morphology in patients with dilated cardiomyopathy (DCM). The
259 mRNA of several mitochondrial proteins is involved in myocardial adenosine triphosphate
260 (ATP) production in patients with DCM. Mitochondrial ATP production is mainly generated
261 by the tricarboxylic acid cycle in the mitochondrial matrix and the electron transport chain in
262 the mitochondrial membrane. Electron microscopic findings have shown that the severity of
263 degeneration of mitochondria cristae in the myocardium is correlated with myocardial ^{99m}Tc -
264 MIBI washout (25). An increase in ^{99m}Tc -MIBI washout was observed in heart failure and

265 ischemic patients with low LV ejection fraction and patients with congestive heart failure and
266 low ^{99m}Tc-MIBI uptake (26,27). Ono *et al.* reported that an increased ^{99m}Tc-MIBI washout was
267 observed in cases of coronary spastic angina, suggesting that the ability of cardiomyocytes to
268 retain the tracer is impaired in viable but damaged myocardium. They also reported that
269 appropriate treatment improves cardiac function and reduces ^{99m}Tc-MIBI washout (28).

270 LGE reflects myocardial fibrosis and indicates irreversible and advanced myocardial
271 impairment (7–9, 16). There is a significant overlap between LGE and infarction, as defined
272 by histology (29). Moreover, mitochondrial abnormalities might provoke myocardial fibrotic
273 remodeling and dysfunction through alterations in intracellular calcium signaling. Fibrotic
274 changes in the myocardium are observed in advanced stages of mitochondrial damage. (30, 31).
275 Thus, it has been suggested that mitochondrial dysfunction occurs in cardiomyopathy, and
276 ^{99m}Tc-MIBI washout, abnormal ^{99m}Tc-MIBI uptake, and LGE are observed, depending on the
277 severity of myocardial impairment.

278 In this study, we classified the segments according to abnormal ^{99m}Tc-MIBI uptake in the
279 early-rest images and washout. Myocardial damage in the segments progressed from groups 1
280 to 4. Thus, there was a tendency for the frequency of LGE to increase from groups 1 to 4. Even
281 in segments with normal ^{99m}Tc-MIBI uptake in early-rest images, some segments showed ^{99m}
282 Tc-MIBI washout. These segments should have also had positive LGE. However, LGE

283 frequency in these segments was less than that in segments with ^{99m}Tc -MIBI washout. LGE
284 frequency is associated with a ^{99m}Tc -MIBI uptake and washout. LGE on cardiac MRI is
285 generally recognized as a useful examination to assess the degree of myocardial disorder in
286 cardiomyopathy (6). While evaluating the clinical stage of cardiomyopathy, we observed that
287 as myocardial damage progresses, ^{99m}Tc -MIBI washout increases first, followed by an
288 abnormal ^{99m}Tc -MIBI uptake, with LGE finally appearing. Therefore, adding delayed-rest
289 ^{99m}Tc -MIBI images and washout assessments may provide additional pathophysiological
290 information in patients with cardiomyopathy.

291 Several limitations are associated with this study. First, this retrospective study was
292 performed at a single institution, and the small sample size did not permit the assessment of
293 the prognostic value of the ^{99m}Tc -MIBI uptake and LGE on MRI in cardiomyopathy. We
294 investigated cardiomyopathy as a whole and have not conducted any disease-specific studies.
295 The correlation of the within-patient segments was not adjusted for in this analysis. This is
296 common in studies with a small population. The gold standard imaging technique for
297 myocardial impairment is LGE, which evaluates fibrosis. In this study, we showed that early-
298 and delayed-rest ^{99m}Tc -MIBI SPECT imaging might be able to assess early myocardial
299 impairment; however, there is insufficient clinical consensus regarding the significance of
300 ^{99m}Tc -MIBI washout. Multimodal imaging may help evaluate the progression of mitochondrial

301 damage in the myocardium, leading to fibrosis. We believe that ^{99m}Tc-MIBI washout reflects
302 early impairment while LGE reflects advanced impairment. However, we did not examine the
303 changes over time, nor their relationship with clinical stage. Furthermore, myocardial
304 impairment, fibrosis, and mitochondrial function were not examined pathologically or
305 immunohistochemically. In this study, the ^{99m}Tc-MIBI uptake abnormality was visually
306 evaluated for all early- and delayed-rest images, and the washout was calculated from the defect
307 score. Since the presence or absence of ^{99m}Tc-MIBI washout was not determined by directly
308 comparing the early- and delayed-rest images, the result may have differed from that of direct
309 evaluation of washout. Additionally, the relationship between the fill-in, which showed an
310 increase in tracer uptake from early to delayed-rest images, and LGE was not evaluated.
311 Segments with ^{99m}Tc-MIBI fill-in (classified as group 5 in this study) were evident in patients
312 with acute myocardial infarction after successful coronary revascularization (2, 32). However,
313 the clinical significance of acquiring images of ^{99m}Tc-MIBI fill-in has not been completely
314 established. The number of segments classified as group 5 was extremely small, and its
315 significance was difficult to evaluate.

316 To our knowledge, this study is the first to identify the relationship of ^{99m}Tc-MIBI uptake
317 abnormality, ^{99m}Tc-MIBI washout, and LGE with MRI. The evaluation of ^{99m}Tc-MIBI washout
318 by rest perfusion scintigraphy using ^{99m}Tc-MIBI can be performed easily as a routine

319 examination for diagnosing cardiomyopathy. Furthermore, detecting early-stage myocardial
320 impairment by evaluating ^{99m}Tc -MIBI washout may increase the possibility of an early
321 diagnosis of cardiomyopathy and lead to more effective treatments.

322 **Conclusion**

323 An abnormal ^{99m}Tc -MIBI uptake reflects mitochondrial dysfunction. Early and delayed ^{99m}Tc -
324 MIBI SPECT is useful in diagnosing earlier myocardial damage stages, which cannot be
325 detected using the standard one-time acquisition of early-rest ^{99m}Tc -MIBI images. LGE can
326 demonstrate tissue fibrosis in advanced stages of myocardial damage. The severity of
327 myocardial damage and clinical stage of cardiomyopathy can be evaluated using ^{99m}Tc -MIBI
328 early/delayed-rest images and cardiac MRI.

329

330

331 **References**

- 332 1. Piwnica-Worms D, Kronauge JF. Uptake and retention of hexakis (2-methoxyisobutyl
333 isonitrile) technetium(I) in cultured chick myocardial cells. Mitochondrial and plasma
334 membrane potential dependence. *Circulation*. 1990 82:1826-38.
- 335
- 336 2. Takeishi Y, Sukekawa H, Fujiwara S, Ikeno E, Sasaki Y, Tomoike H, et al. Reverse
337 redistribution of technetium-99m-sestamibi following direct PTCA in acute myocardial
338 infarction. *J Nucl Med* 1996; 37:1289–94
- 339
- 340 3. Piwnica-Worms D, Chiu ML, Kronauge JF. Divergent kinetics of ²⁰¹Tl and ^{99m}Tc-
341 SESTAMIBI in cultured chick ventricular myocytes during ATP depletion. *Circulation*. 1992;
342 85:1531–41.
- 343
- 344 4. Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M. A novel clinical indicator using Tc-
345 ^{99m} sestamibi for evaluating cardiac mitochondrial function in patients with cardiomyopathies.
346 *J Nucl Cardiol*. 2007; 14:215–20.
- 347

348 5. Matsuo S, Nakajima K, Kinuya S. Evaluation of cardiac mitochondrial function by a
349 nuclear imaging technique using technetium-99m-mibi uptake kinetics. *Asia Ocean J Nucl*
350 *Med Biol.* 2013; 1:39-43.

351

352 6. H. Mahrholdt, A. Wagner, R.M. Judd, U. Sechtem, R.J. Kim. Delayed enhancement
353 cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur*
354 *Heart J*, 2005; 26:1461-74

355

356 7. Kramer CM. Role of Cardiac MR imaging in cardiomyopathies. *J Nucl Med.* 2015; 56:39S–
357 45S.

358

359 8. Simonetti OP, Kim RJ, Fieno DS, Hillenbrand HB, Wu E, Bundy JM, et al. An improved
360 MR imaging technique for the visualization of myocardial infarction. *Radiology.* 2001;
361 218:215–23.

362

363 9. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium
364 enhancement in clinical outcomes for hypertrophic cardiomyopathy. *JACC Cardiovasc*
365 *Imaging.* 2012; 5:370–377.

- 366 10. Yuki H, Utsunomiya D, Shiraishi S, Takashio S, Sakamoto F, Tsuda N et al. Correlation
367 of left ventricular dyssynchrony on gated myocardial perfusion SPECT analysis with extent
368 of late gadolinium enhancement on cardiac magnetic resonance imaging in hypertrophic
369 cardiomyopathy. *Heart Vessels*. 2018; 33:623-29.
- 370 11. Wang L, Yan C, Zhao S, Fang W. Comparison of (99m)Tc-MIBI SPECT/18F-FDG PET
371 imaging and cardiac magnetic resonance imaging in patients with idiopathic dilated
372 cardiomyopathy: assessment of cardiac function and myocardial injury. *Clin Nucl Med*.
373 2012; 37:1163-9
- 374 12. Masuda A, Yoshinaga K, Naya M, Manabe O, Yamada S, Iwano H, et al. Accelerated
375 (99m)Tc-sestamibi clearance associated with mitochondrial dysfunction and regional left
376 ventricular dysfunction in reperfused myocardium in patients with acute coronary syndrome.
377 *EJNMMI Res*. 2016; 6: 41
- 378 13. Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P. Multimodality image
379 registration by maximization of mutual information. *IEEE Trans Med Imaging*. 1997;
380 16:187–98.
- 381
- 382 14. Lin GS, Hines HH, Grant G, Taylor K, Ryals C. Automated quantification of myocardial

383 ischemia and wall motion defects by use of cardiac SPECT polar mapping and 4-dimensional
384 surface rendering. J Nucl Med Technol. 2006; 34:3–17.

385 15. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al.
386 Standardized myocardial segmentation and nomenclature for tomographic imaging of the
387 heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the
388 Council on Clinical Cardiology of the American Heart Association. Circulation.
389 2002 ;105:539-42.

390 16. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-
391 enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl
392 J Med. 2000; 343: 1445-53.

393

394 17. Bondarenko O, Beek AM, Hofman MB, Kühl HP, Twisk JW, van Dockum WG et al.
395 Standardizing the definition of hyperenhancement in the quantitative assessment of infarct
396 size and myocardial viability using delayed contrast-enhanced CMR. J Cardiovasc Magn
397 Reason 2005; 7:481–5.

398

399 18. Kitabatake A, Tomoike H. Cardiomyopathy: Diagnostic guidelines and commentary.
400 Research Group on Idiopathic Cardiomyopathy, Intractable Disease Research Project of the

401 Japanese Ministry of Health, Labor and Welfare. Sapporo: Karinsha Co., Ltd., 2005 (in
402 Japanese)

403

404 19. Yoshida A, Takano H, Asai K, Yasutake M, Amano Y, Kumita S, et al. Comparison of
405 perfusion-metabolism mismatch in ^{99m}Tc-MIBI and ^{123I}-BMIPP scintigraphy with cardiac
406 magnetic resonance in patients with dilated cardiomyopathy. *J Card Fail.* 2013; 19:445-53

407

408 20. Carvalho PA, Chiu ML, Kronauge JF, Kawamura M, Jones AG, Holman BL et al.
409 Subcellular distribution and analysis of technetium-^{99m}-MIBI in isolated perfused rat hearts.
410 *J Nucl Med.* 1992; 33:1516-22.

411

412 21. Sekiguchi M, Konno S. Diagnosis and classification of primary myocardial disease with
413 the aid of endomyocardial biopsy. *Jpn Circ J.* 1971;35:737-54.

414

415 22. Sarai M, Morimoto S. Washout Rate of ^{99m}Tc-MIBI myocardial scintigraphy in cardiac
416 sarcoidosis. *The Japanese Journal of Sarcoidosis and Other Granulomatous Disorders.* (in
417 Japanese) 2012; 32: 60-64

418

419 23. Chung YW, Kang SM Mitochondrial dysfunction is involved in the pathological process
420 of cardiomyopathy. *BMB Rep.* 2015; 48: 541–8.
421

422 24. Lee SR, Han J. Mitochondrial Mutations in Cardiac Disorders. *Adv Exp Med Biol.* 2017;
423 982:81-111.
424

425 25 Hayashi D, Ohshima S, Isobe S, Cheng XW, Unno K, Funahashi H et al. Increased 99m
426 Tc-sestamibi washout reflects impaired myocardial contractile and relaxation reserve during
427 dobutamine stress due to mitochondrial dysfunction in dilated cardiomyopathy patients. *J Am
428 Coll Cardiol.* 2013; 61:2007-17.
429

430 26. Kumita S, Seino Y, Cho K, Nakajo H, Toba M, Fukushima Y, et al. Assessment of
431 myocardial washout of Tc-99m-sestamibi in patients with chronic heart failure: comparison
432 with normal control. *Ann Nucl Med.* 2002; 16:237–42.
433

434 27. Sugiura T, Takase H, Toriyama T, Goto T, Ueda R, Dohi Y. Usefulness of Tc-99m
435 methoxy isobutyl isonitrile scintigraphy for evaluating congestive heart failure. *J Nucl
436 Cardiol.* 2006; 13:64–8.

437

438 28. Ono S, Takeishi Y, Yamaguchi H, Abe S, Tachibana H, Sato T, et al. Enhanced regional
439 washout of technetium-99m-sestamibi in patients with coronary spastic angina. *Ann Nucl*
440 *Med.* 2003; 17:393–8.

441

442 29. Rehwald WG, Fieno DS, Chen EL, Kim RJ, Judd RM. Myocardial magnetic resonance
443 imaging contrast agent concentrations after reversible and irreversible ischemic injury.
444 *Circulation.* 2002; 105:224–229.

445

446 30. Norton M, Ng AC, Baird S, Dumoulin A, Shutt T, Mah N, et al. ROMO1 is an essential
447 redoxdependent regulator of mitochondrial dynamics. *Sci Signal.* 2014;7:ra10.

448

449 31. Torrealba N, Aranguiz P, Alonso C, Rothermel BA, Lavandero S. Mitochondria in
450 Structural and Functional Cardiac Remodeling. *Adv Exp Med Biol.* 2017; 982:277-306.

451

452 32. Fujiwara S, Takeishi Y, Atsumi H, Yamaki M, Takahashi N, Yamaoka M, et al. Prediction
453 of functional recovery in acute myocardial infarction: comparison between sestamibi reverse
454 redistribution and sestamibi/BMIPP mismatch. *J Nucl Cardiol* 1998; 5:119-127.

455

456

457

458

459 **Acknowledgment**

460 The authors are grateful to Keiichiro Yoshinaga MD, PhD, for suggesting helpful advice and

461 performing critical revision. We would like to offer our profound gratitude.

462

463 **Funding**

464 **None**

465

466 **Conflicts of interest**

467 The authors declare no conflicts of interest.

468

469 **Figure legends**

470 **Figure 1** ^{99m}Tc-MIBI single-photon emission computerized tomography (SPECT) and
471 magnetic resonance imaging (MRI) analyses. a: left ventricular wall was divided into 17
472 segments. b: ^{99m}Tc-MIBI SPECT in the early and delayed phase. c: Late gadolinium
473 enhancement (LGE) on MRI at the basal and mid-level of the left ventricle. d: Polar map
474 showing LGE spread in each segment analyzed by Ziostation. e: Summary of analysis results.

475

476 **Figure 2** Typical case of early-stage cardiomyopathy. An 81-year-old woman was diagnosed
477 with takotsubo cardiomyopathy. Echocardiogram revealed systolic dysfunction (ejection
478 fraction 46%, end diastolic volume 85 mL, end systolic volume 46 mL). The left ventricular
479 wall motion was severely hypokinetic from the middle to the apex. ^{99m}Tc-MIBI single-photon
480 emission computerized tomography (SPECT) and cardiac magnetic resonance imaging (MRI)
481 were performed within three days. On SPECT, ^{99m}Tc-MIBI uptake was decreased in a small
482 area of the anteroseptal and inferior wall. Increased washout in the wide area of the middle to
483 the apex is shown. No late gadolinium enhancement (LGE) is noted.

484

485 **Figure 3** Typical case of advanced cardiomyopathy. A 59-year-old man was diagnosed with
486 cardiac sarcoidosis. Echocardiogram revealed lower normal systolic function (ejection fraction

487 50%, end diastolic volume 94 mL, end systolic volume 47 mL). The left ventricular wall
488 motion was akinetic from the base to the middle of the anteroseptal wall, and mild dyskinesia
489 was observed in the inferior wall. ^{99m}Tc-MIBI single-photon emission computerized
490 tomography (SPECT) and cardiac magnetic resonance imaging (MRI) were performed within
491 three days. On SPECT, ^{99m}Tc-MIBI uptake decreased from the base of the anterior wall to the
492 septum. Increased washout from the middle to the apex of the anterior wall, septum, and the
493 inferior wall is shown. Late gadolinium enhancement (LGE) in a wide area from the anterior
494 wall to the septum and a small area of the inferior wall is shown.

495

496

497 **Tables**

498 **Table 1 Patients' Characteristics**

Parameter	Data
Gender (n), Male/Female	13/8
Age (years) Mean±SD/range	60±13 (28-82)
Body weight (Kg) Mean±SD/range	62.9±17.7 (41-100)
Cardiac function indices	
End-diastolic volume (ml) mean±SD/range	146.5±69.6 (64-254)
End-systolic volume (ml) mean±SD/range	80.5±56.4 (22-166)
Ejection fraction (%) mean±SD/range	49.4±15.5 (26-72)
Type of cardiomyopathy	
Sarcoidosis/hypertensive/DCM/takotsubo/HCM/toxic	8/5/4/2/1/1

499 The cardiac function indices were calculated by quantitative gated single-photon emission
 500 computed tomography.

501 DCM: dilated cardiomyopathy, HCM: hypertrophic cardiomyopathy, Hypertensive:
 502 hypertensive cardiomyopathy, Sarcoidosis: cardiac sarcoidosis, SD: standard deviation,
 503 Takotsubo: takotsubo cardiomyopathy, toxic: toxic cardiomyopathy

504

505

506

507

508

509

510

511

512

513 **Table 2 Relationship between ^{99m}Tc-MIBI washout and LGE.**

	LGE negative	LGE positive	Total
Washout negative	163(71.5%)	65(28.5%)	228
Washout positive	69(63.9%)	39(36.1%)	108

514 LGE, late gadolinium enhancement
515 MIBI, ^{99m}Tc-methoxy-isobutyl-isonitrile
516 Fisher's exact test: p = 0.165

517

518

519

520 **Table 3 Myocardial Perfusion Defect with Early Rest Images of ^{99m}Tc-MIBI**

Defect Score	Numbers	LGE (negative)	LGE (positive)
	n (column %)		n (row %)
0	168 (50%)	139	29 (17.2%)
1	96 (28.5%)	62	34 (35.4%)
2	42 (12.5%)	24	18 (42.8%)
3	21 (6.3%)	5	16 (76.1%)
4	9 (2.7%)	2	7 (77.8%)

521 defect score: 0, normal uptake; 1, mildly decreased; 2, moderately decreased; 3, severe

522 decreased; 4, perfusion defect

523 LGE, late gadolinium enhancement

524 Fisher's exact test: $p < 0.001$.

525

526

527 **Table 4 Segments with Normal ^{99m}Tc-MIBI Perfusion in Early Rest Images.**

Group	LGE (negative)	LGE (positive)	Total
Group 1	93 (80.2%)	13 (19.8%)	106
Group 2	46 (74.2%)	16 (25.8%)	62

528 LGE, late gadolinium enhancement

529 MIBI, ^{99m}Tc-methoxy-isobutyl-isonitrile

530 Fisher's exact test: p = 0.033

531

532

533 **Table 5 Segments with ^{99m}Tc-MIBI uptake decrease in Early Rest Images.**

Group	LGE (negative)	LGE (positive)	Total
Group 3	58 (57.4%)	43 (42.5%)	101
Group 4	23 (50%)	23 (50%)	46

534 LGE, late gadolinium enhancement
535 MIBI, ^{99m}Tc-methoxy-isobutyl-isonitrile
536 Fisher's exact test: p = 0.475

537
538
539
540
541
542
543
544
545
546
547
548
549
550
551

Figure.1

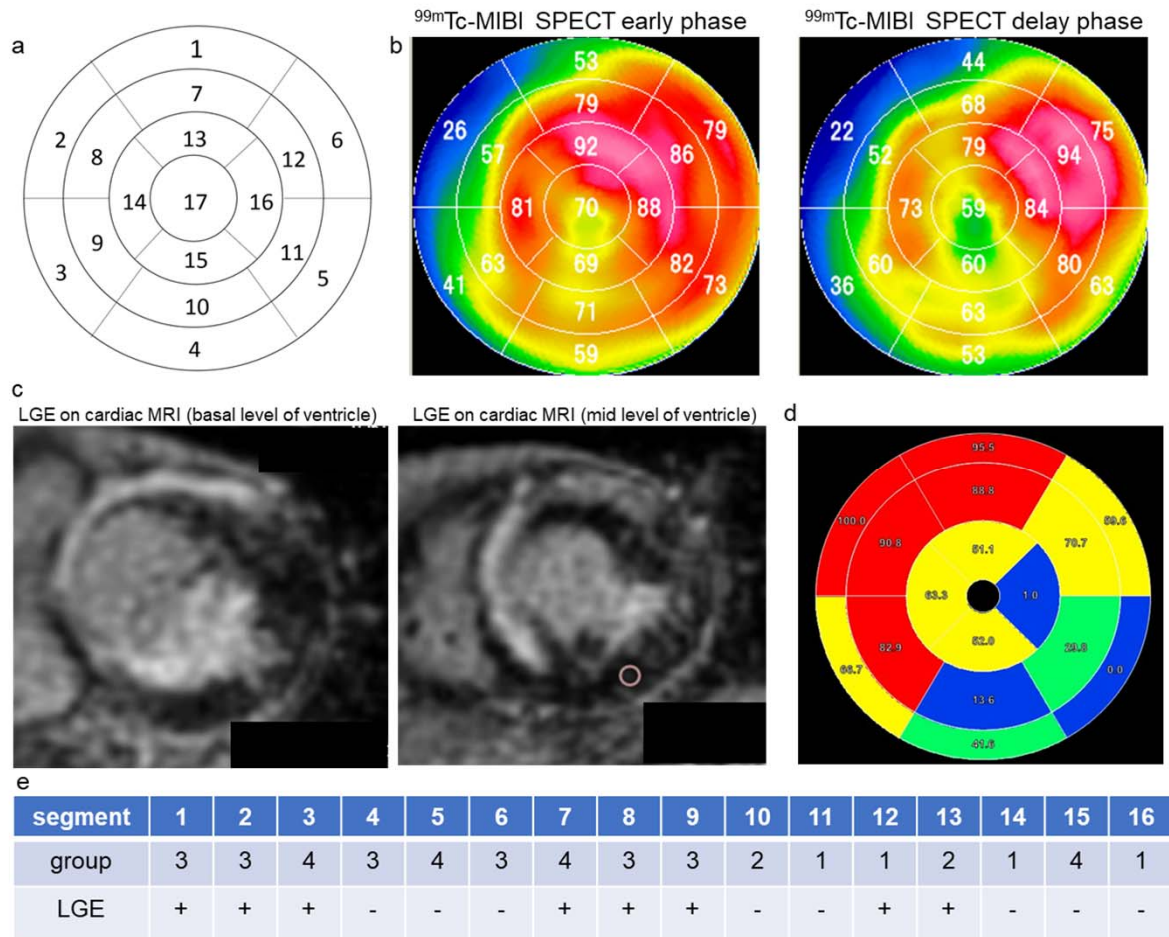


Figure.3

