

## Comparative study of $^{201}\text{Tl}$ -scintigraphic image and myocardial pathologic findings in patients with dilated cardiomyopathy

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The objective of the present study was to characterize the production of  $^{201}\text{Tl}$  myocardial perfusion defects, the relation between the  $^{201}\text{Tl}$  multiple small defects and the myocardial damage indicated by myocardial fibrosis shown histopathologically in patients with dilated cardiomyopathy (DCM).

Rest  $^{201}\text{Tl}$  scintigraphy was performed in thirty-seven patients with myocardial tissue fibrosis by endomyocardial biopsy, and without stenosis of the coronary artery.  $^{201}\text{Tl}$  myocardial SPECT images were visually classified into 4 grades according to the severity of inhomogeneous perfusion defects (IPD), 0: none, 1: slight, 2: moderate, 3: severe.  $^{201}\text{Tl}$  uptake, defect regions (DR), and coefficient of variation % (CV%) were also quantified by Bull's eye quantification in nineteen patients. During cardiac catheterization, three biopsy specimens were obtained from the lateral wall to the apical region of the left ventricle and the amount of fibrosis was assessed by means of light microscopic morphometry. The myocardial fibrosis was also classified into 4 grades by a point-counting method. Autopsy study was also assessed in six patients.  $^{201}\text{Tl}$  perfusion defects were observed in 35 (94.6%) patients, of whom 29 (78.4%) showed inhomogeneous perfusion defects. Twenty-four (64.9%) showed Stage 0 and 1  $^{201}\text{Tl}$  findings, and 21 (62.2%) had myocardial fibrosis in stage 1. Clinically, the correlation between the grades of the IPD, %  $^{201}\text{Tl}$  uptake, DR and CV% of myocardial uptake, which were calculated semiquantitatively by Bull's eye image, and the histological grades of fibrosis were also good (IPD vs. fibrosis:  $r = 0.7014$ ; %  $^{201}\text{Tl}$  uptake vs. fibrosis:  $r = -0.6542$ ; DR vs. fibrosis:  $r = 0.7027$ ; CV% vs. fibrosis:  $r = 0.6985$ ). The  $^{201}\text{Tl}$  SPECT findings were in close agreement with the severity of myocardial fibrosis confirmed by autopsy, but the grading of the IPD was not related to the ejection fraction or left ventricular diameter.

It showed a higher rate of inhomogeneous  $^{201}\text{Tl}$  myocardial perfusion defects (78.4%) in patients with DCM. This result may contribute to the clinical evaluation of DCM or differentiation from other diseases. Furthermore, the grading of  $^{201}\text{Tl}$  inhomogeneous perfusion defects related to the myocardial fibrosis of left ventricular myocardium may contribute to speculation of the myocardial degenerative stage in clinical settings.

**Key words:** dilated cardiomyopathy (DCM),  $^{201}\text{Tl}$ -SPECT, myocardial fibrosis.

### INTRODUCTION

THALLIUM-201 myocardial single photon emission computed tomography ( $^{201}\text{Tl}$  SPECT) is often reported to show multiple perfusion defects in patients with dilated

cardiomyopathy (DCM) which are different from the defects observed in coronary artery disease.<sup>1,2</sup> There have also been studies on the methods to express the defect patterns and the degrees of abnormal uptake on  $^{201}\text{Tl}$  myocardial SPECT imaging.<sup>3</sup> The autopsy studies with DCM showed that the percentage of fibrosis in the left ventricular wall was significantly greater than that with secondary eccentric hypertrophy or normal heart,<sup>4,5</sup> and there was significant relationship between % fibrosis and  $^{201}\text{Tl}$  defect in the non-uniform pattern high fibrosis group,

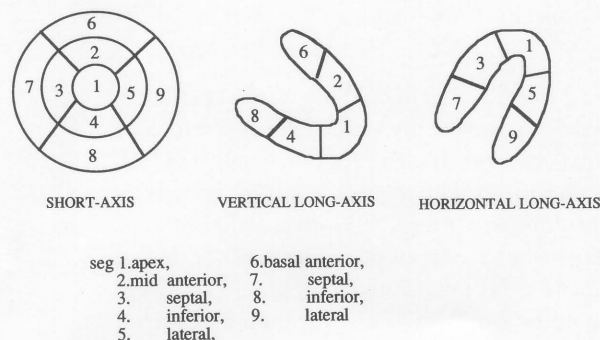
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**Table 1** Clinical findings and profile in patients with dilated cardiomyopathy

	TI-201 score	Bull's eye
Patients (numbers)	37	19
F/M	12/25	4/15
Age	49 ± 16	50 ± 16
LVEF (%)	35.3 ± 9.8	37.5 ± 9.9
LVDd (mm)	63.8 ± 6.2	65.3 ± 5.1
TI-201 % uptake	—	61.2 ± 18.1
DR (pixels)	—	137 ± 53.5
%CV	—	13.2 ± 3.7

LVEF = left ventricular ejection fraction, LVDd = left ventricular diastolic dimension, DR = defect region pixels, %CV = % coefficient of variation



**Fig. 1** Schematic presentation of nine myocardial segments in short-axis, vertical long-axis and horizontal long-axis slice.

and the areas with a high incidence of % fibrosis showed  $^{201}\text{Tl}$  defects.<sup>6</sup> But there is no study on the relationships of histopathologic fibrosis of biopsy to the degrees and patterns of SPECT imaging. Sufficient data on the correspondence between  $^{201}\text{Tl}$  imaging and histopathological findings are needed for the solution of this problem. The purposes of the present study are 1) to describe the patterns of thallium scintigraphy in patients with dilated cardiomyopathy, and 2) to correlate the scintigraphic findings with endomyocardial biopsy findings.

## METHODS

### Patients:

The study group comprised 37 patients (25 male and 12 female, mean age  $49 \pm 16$  years old) with DCM. The subjects were the patients admitted to the Third Department of Internal Medicine, Kyoto University Hospital, from 1987 to 1995, and were diagnosed as having DCM on the basis of the history, chest X-rays, ECG, echocardiography and left ventriculography. The diagnosis of DCM was suspected when patients had an increased cardiothoracic ratio and unexplained congestive heart failure. Echocardiography and catheterization data supported DCM, when they showed diffuse hypokinesis in wall motion and normal coronary arteries without valvular heart disease. The final decision was made when biopsy

**Table 2** TI-201 SPECT and left ventricular biopsy findings in patients with DCM.

Stage	TI-201 score (Bec) numbers	% (Bec)	left ventricular fibrosis (Bec) numbers	% (Bec)
0	2 (0)	5.4 (0)	0 (0)	0 (0)
1	22 (11)	59.5 (57.9)	23 (12)	62.2 (63.2)
2	7 (4)	18.9 (21.1)	9 (3)	24.3 (15.7)
3	6 (4)	16.2 (21.1)	5 (4)	13.5 (21.1)

Bec = Bull's eye cases



**Fig. 2** Representative  $^{201}\text{Tl}$ -SPECT image showing the stage of inhomogeneous perfusion defect with DCM.

findings showed cellular loss and fibrosis.<sup>7</sup> Patients with complications such as arrhythmia were included. Patients underwent  $^{201}\text{Tl}$  SPECT within  $9 \pm 5$  weeks before left ventricular biopsies without intercurrent changes in their clinical status. The left ventricular ejection fraction was determined by the Kennedy's<sup>8</sup> method by left ventriculography obtained by cardiac catheterization. The left ventricular end-diastolic dimension was determined in the left ventricular long-axial view of standard two-dimensional echocardiography at the level of the papillary muscles (Table 1).

### $^{201}\text{Tl}$ imaging:

Resting  $^{201}\text{Tl}$  myocardial SPECT was performed for all the patients after a 12 hour fast. After 15 minutes of intravenous  $^{201}\text{Tl}$  injection with 74–111 MBq (2–3 mCi), SPECT scans were obtained with a gamma camera equipped with a General Electric 400 AC/T linked to a MaxiStar computer before 1990. After 1990, SPECT imaging was performed with General Electric Medical

**Table 3** Autopsy findings in patients with DCM

No.	Sex	Age	Tl-201 score	Fibrosis (LV)	LVEF(%)	LVDd (mm)	Died after Tl-201 (months)
1	M	43	+++ (ant, sep, inf)	+++ (ant, sep)	32.5	70	16
2	M	75	++	++	41.3	67	20
3	F	61	+	+	31.8	72	17
4	F	67	+++ (ant)	+++ (ant)	25.8	71.9	31
5	F	60	+	+	28	61	30
6	M	58	+	++	20	73	11

LVEF = left ventricular ejection fraction, LVDd = left ventricular diastolic dimension, ant = anterior, sep = septal, inf = inferior

Systems Limited Albans Heart England, linked to a YNO 189 YOKOKAWA Medical System. Collimator used was a low-energy and general purpose type. Data were collected from 32 views of 30 sec each over 180° from the 45° right anterior oblique angle to the 45° left posterior oblique angle. Oblique tomograms parallel to the long- and short-axis of the left ventricle were also reconstructed. For<sup>9,10</sup> nineteen of them the Bull's eye map quantification (15 males and 4 females, 50 ± 16 years old) was serially performed. In the other patients, the Bull's eye map quantification could not be performed because the computer system was different.

#### Quantitative image analysis:

For each study, the left ventricular myocardium was divided into nine segments on the SPECT images and polar map display (basal anterior, septal, inferior, lateral, middle anterior, septal, inferior, lateral and apical) to assess the <sup>201</sup>Tl score (Fig. 1). The perfusion defect of <sup>201</sup>Tl tracer in each segment was scored by the consensus of the three experienced observers using a four-point grading system, 0: normal, 1: slight inhomogeneous perfusion abnormality (multiple small hypoperfusion), 2: moderate inhomogeneous defect (multiple small defect within the size of 1 segment. The stage is between 1 and 3), and 3: severe inhomogeneous defect or larger defect (multiple large defect greater than 1 segment or a quite large solitary defect)<sup>3,9</sup> without having any information about the patients (Fig. 2). For quantitative analysis, a circumferential profile curve was generated from apical to basal short-axial slices to a Bull's eye polar map with 100% as the maximum count in each <sup>201</sup>Tl image. Defect regions (DR), that were <sup>201</sup>Tl uptake < 80% in the nine myocardial segments were set manually on the <sup>201</sup>Tl image. Defect regions were defined as those with a total size of <sup>201</sup>Tl uptake < 80% in the nine myocardial segments. Within each region of interest, the mean % <sup>201</sup>Tl uptake of the tracer which was <sup>201</sup>Tl uptake < 80% in nine myocardial segments were calculated. The coefficient of variance % (CV%) was calculated as standard deviation / mean × 100.<sup>10-15</sup>

#### Left ventricular biopsies:

Myocardial biopsy was performed from the left ventricular endocardium during cardiac catheterization in all subjects. Three biopsy specimens were obtained from the area of the left ventricle from the lateral wall to the apical region. Myocardial slices were stained by Masson's Trichrome. Morphometric evaluations were performed by two investigators, who were unaware of the patients scintigraphic data, and the amount of fibrosis was assessed by standard light microscopy. The ratio of the fibrotic area to the total tissue area was calculated as the percent area of fibrosis (%F), and the severity of left ventricular fibrosis (LVF) was graded histopathologically from Stage 0 to Stage 3 (0 = trivial; %F from 0 to 25%, 1 = mild %F from 26 to 50%, 2 = moderate; %F from 51 to 75%, 3 = severe; %F > 75%) (Fig. 3). The severity of endocardial fibrosis was studied by autopsy in 6 patients who died of DCM (3 males and 3 females, mean age 61 ± 5 years).

#### STATISTICAL ANALYSIS

Data are given as the mean ± SD. Comparison between the regression lines was performed by student's *t* test. The correlation between the <sup>201</sup>Tl score and left ventricular fibrosis (LVF) was determined from linear regression analysis. Correlations with the % <sup>201</sup>Tl uptake vs. LVF, DR vs. LVF, CV% vs. LVF, <sup>201</sup>Tl score vs. LVEF and <sup>201</sup>Tl score vs. LVDd were calculated by the (nonparametric) Spearman's rank statistics. For all tests, a value *p* < 0.05 was considered indicative of a statistically significant difference.

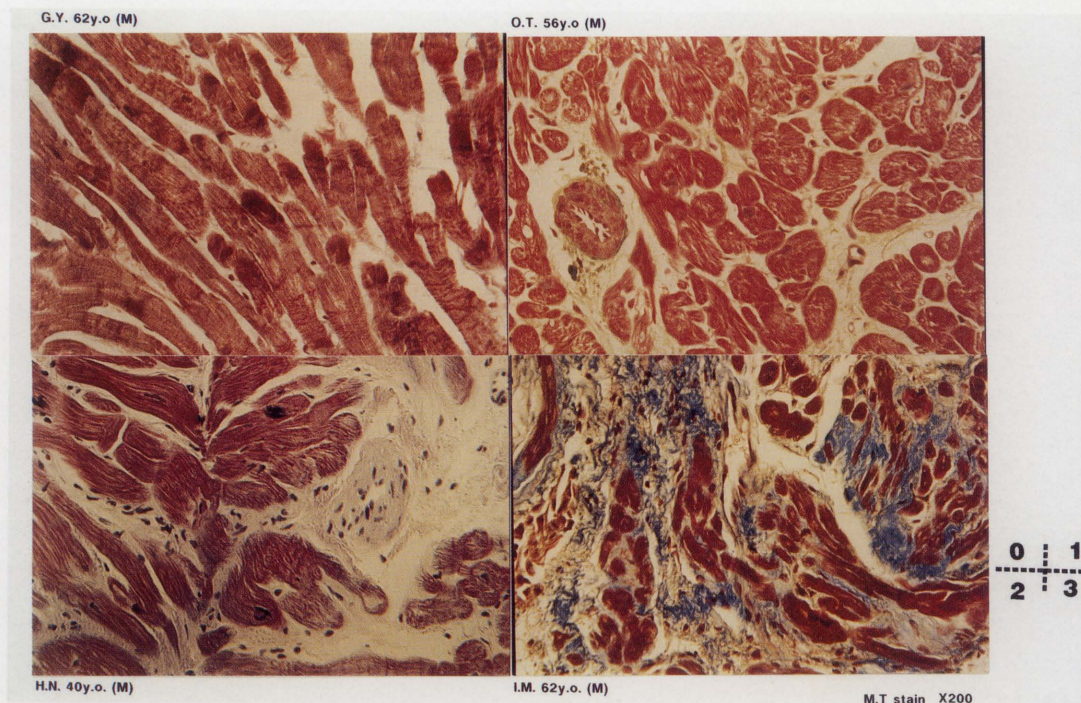
#### RESULTS

##### Relation between <sup>201</sup>Tl SPECT imaging and myocardial biopsy:

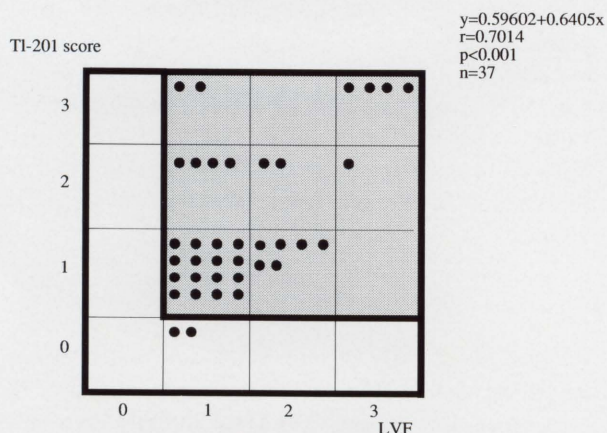
Of the 37 patients, <sup>201</sup>Tl perfusion defects were observed in 35 (94.6%) patients, of whom 29 (78.4%) had inhomogeneous defects, 2 patients (5.4%) had normal perfusion and 6 (16.2%) had larger defects. Stages 0 and 1 were the most frequent in 24 (64.8%) patients.

Myocardial fibrosis was demonstrated by histological





**Fig. 3** Stage of endomyocardial fibrosis assessed by left ventricular biopsy in DCM (Masson's Trichrome stain.  $\times 200$ )



**Fig. 4**  $^{201}\text{Tl}$  score and left ventricular biopsy findings (number of patients), LVF = left ventricular fibrosis.

examination of biopsy specimens in 34 (100%), and 23 (62.2%) of the patients in stage 1. Stage 2 and stage 3 were less frequent (37.8%). The correlation between the grading of  $^{201}\text{Tl}$  SPECT findings and the biopsy staging of fibrosis was good ( $r = 0.7014$ ,  $p < 0.001$ ) in DCM (Fig. 4). When patients were studied by the quantification of Bull's eye images, the correlation between fibrosis and  $\% ^{201}\text{Tl}$  uptake, DR and CV% were all good (LVF vs.  $\% ^{201}\text{Tl}$  uptake,  $r = -0.6542$ ; LVF vs. DR,  $r = 0.7027$ ; LVF vs. CV%,  $r = 0.6985$ ) (Fig. 5).

**Relationship of  $^{201}\text{Tl}$  SPECT findings to LVEF and LVDd:** The  $^{201}\text{Tl}$  myocardial SPECT stage of inhomogeneity showed no correlation with LVEF ( $r = -0.3241$ ) or LVDd ( $r = 0.2517$ ).

#### Comparison between autopsy findings and $^{201}\text{Tl}$ SPECT findings:

Concerning the 6 patients who died of DCM, Intervals between autopsy and  $^{201}\text{Tl}$  SPECT were 17 to 31 months (mean =  $21.1 \pm 6$  months), and the grading of the  $^{201}\text{Tl}$  perfusion defect was related to autopsy findings (Table 3).

#### Case presentation

**CASE 1** (autopsy No. 1. Fig. 6-a). A 43 year-old-male patient with cardiomyopathy died 16 months after  $^{201}\text{Tl}$  SPECT imaging. The heart weighed 420 g, and the left ventricle was dilated and hypertrophied.  $^{201}\text{Tl}$  SPECT imaging showed noticeable left ventricular enlargement, severe inhomogeneous defect and large perfusion defects in the anterior, septal and inferior segments. Autopsy revealed remarkable massive fibrosis in the same region of the left ventricle.

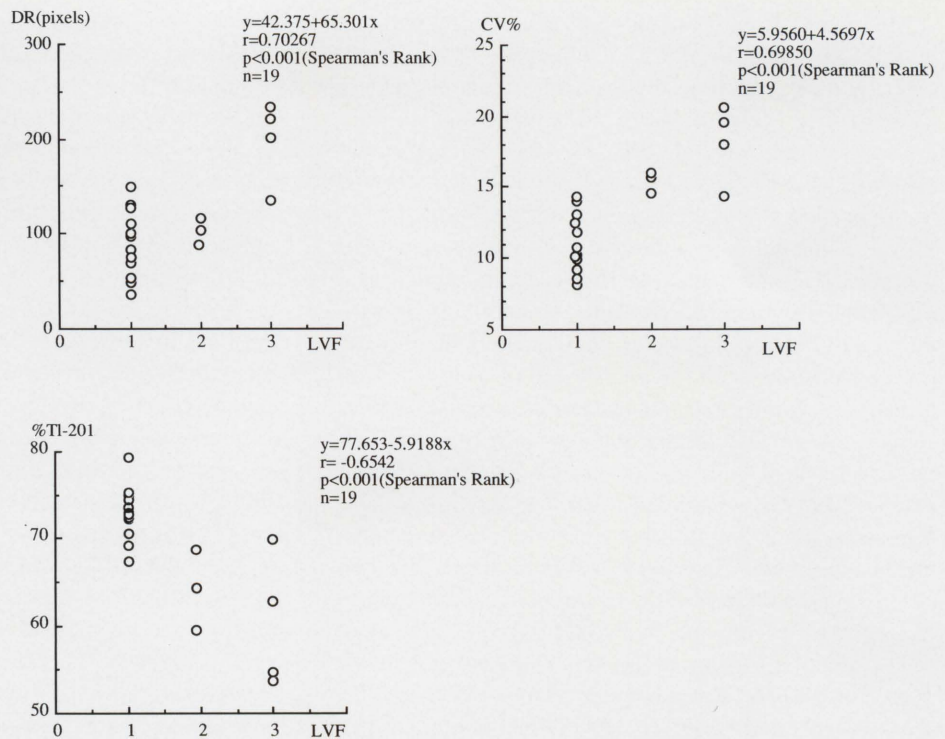
**CASE 2** (autopsy No. 2. Fig. 6-b). A 70-year-old-male with cardiomyopathy died 20 months after  $^{201}\text{Tl}$  SPECT imaging. The heart weighed 520 g, all four chambers were dilated and showed signs of diffuse interstitial fibrosis.  $^{201}\text{Tl}$  SPECT finding in this patient showed dilatation of the left ventricle and moderate inhomogeneous defects.

#### DISCUSSION

Our study indicated that an inhomogeneous  $^{201}\text{Tl}$ -SPECT image will show at least myocardial fibrotic changes depending on the stage of the DCM, by means of a comparative study with endomyocardial biopsy.



**Fig. 5** Relation between the findings of  $^{201}\text{Tl}$  uptake and left ventricular fibrosis (LVF), defect region (DR) and LVF, coefficient of variation (%CV) and LVF, in patients with DCM. %CV = standard deviation/mean  $\times$  100.

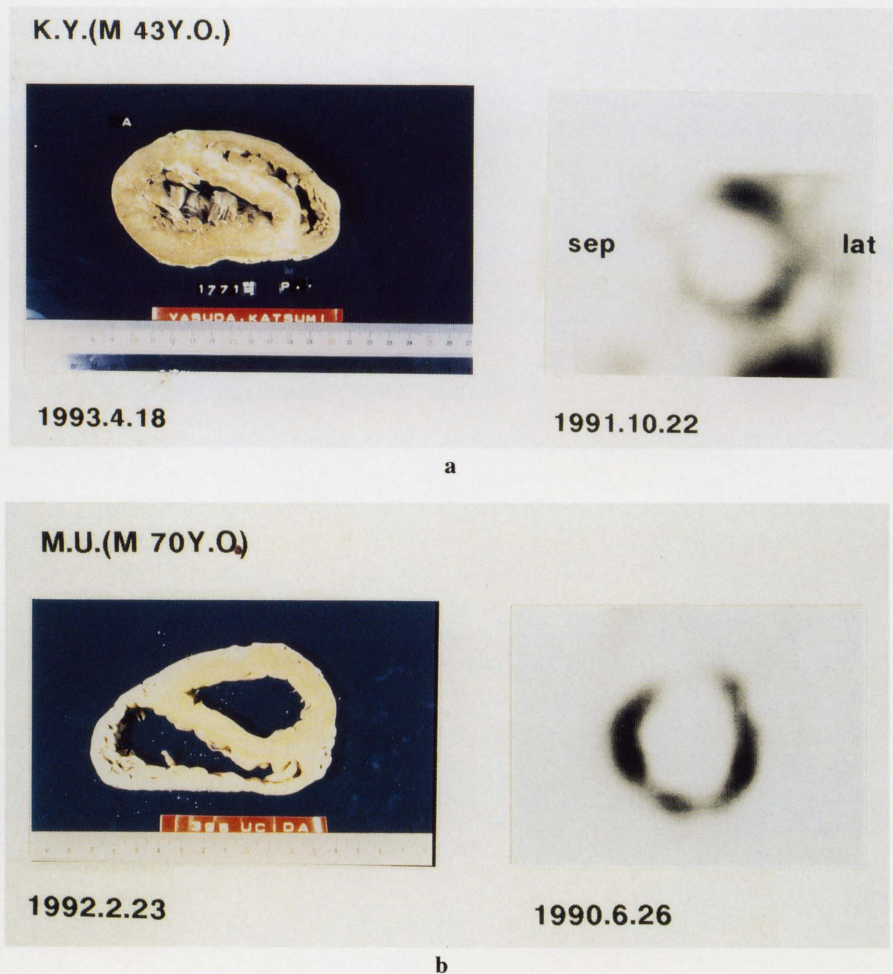


**Fig. 6-a** Transverse section through left ventricle (LV) and short-axis thallium imaging in a 43 years old man (autopsy case No. 1). There were areas of fibrosis from septal to anterior wall, and corresponds to the segments of perfusion defects on the thallium image. Autopsied heart showed right ventricle as right side of the photograph, however,  $^{201}\text{Tl}$  scintigraphy left side. Upper side shows anterior wall on both images.

**Fig. 6-b** Transverse section through the left ventricle (LV) and short-axis thallium imaging in a 70 years old man (autopsy case No. 2). There were diffuse interstitial fibrosis in the left ventricle, and moderate inhomogeneous perfusion defects on the thallium image. Autopsied heart and  $^{201}\text{Tl}$  image show the same projection of image.

*List of abbreviations:*

$^{201}\text{Tl}$  SPECT:  $^{201}\text{Tl}$  single photon emission computed tomography; DCM: dilated cardiomyopathy; IPD: inhomogeneous perfusion defect; LVF: left ventricular fibrosis; %F: % fibrosis; SD: standard deviation; DR: defect regions; CV%: coefficient of variation%; LVEF: left ventricular ejection fraction; LVDd: left ventricular diastolic dimension; ECG: electrocardiogram



There have been previous reports assessing patients with DCM by means of  $^{201}\text{Tl}$  scintigraphy.<sup>1-4</sup> Doi et al.<sup>4</sup> classified dipyridamole myocardial  $^{201}\text{Tl}$  scintigraphy findings into 4 stages, that is, no defect, small solitary defects, multiple small defects, and large defects, showing that 44.2% of the patients had multiple small defects. In the present study, multiple defects were observed in 78.4% of the patients, and the defect pattern was completely different from that observed in myocardial infarction. The causative mechanism underlying the production of  $^{201}\text{Tl}$  perfusion defects in patients with DCM remains obscure with the manifestation of myocardial fibrosis. There have been many theories as to  $^{201}\text{Tl}$  defects such as myocardial degeneration, atrophy, necrosis and ventricular wall thinning. In this study, about 60% of patients were found to have a slight  $^{201}\text{Tl}$  defect and slight fibrosis, and it is possible that some myocardial damage might have been assessed by  $^{201}\text{Tl}$  findings. We had conflicting results regarding the effect of  $^{201}\text{Tl}$  finding to fibrosis. 1) Two patients had slight fibrosis but normal  $^{201}\text{Tl}$  perfusion. It may be for this reason that a lesser degree of fibrosis cannot respond to the  $^{201}\text{Tl}$  uptake. 2) Two patients had severe fixed  $^{201}\text{Tl}$  defects, but lesser degrees of fibrosis. A cause and effect relationship cannot be proved by myocardial fibrosis. It is probable that the production of fixed  $^{201}\text{Tl}$  defects by other factors such as ventricular wall thinning caused by myocardial atrophy or metabolic change may exert fixed  $^{201}\text{Tl}$  defects.

There have been several reports on endomyocardial biopsies and autopsied hearts in patients with DCM.<sup>4,6,16</sup> Yaoita<sup>6</sup> compared histopathological findings in cardiac muscle and myocardial perfusion defects on  $^{201}\text{Tl}$  scintigraphy in ten autopsied cases with DCM. They showed a significant relationship between % fibrosis and  $^{201}\text{Tl}$  defects in a high % fibrosis group, and the areas with a high incidence of % fibrosis showed  $^{201}\text{Tl}$  defects. But Dunn et al.<sup>1</sup> compared the  $^{201}\text{Tl}$  score with autopsy findings in DCM patients and found that the ventricular wall was thin and no fibrosis was observed at the site of  $^{201}\text{Tl}$  defects. In our study, however, the severity of fibrosis of endocardial tissues was in close agreement with the stage of defects in the  $^{201}\text{Tl}$  myocardial scintigrams. We classified  $^{201}\text{Tl}$  defects into 4 stages, and examined the relationships of perfusion defects and defect patterns of  $^{201}\text{Tl}$  myocardial SPECT with left ventricular histopathologic fibrosis. The classification of  $^{201}\text{Tl}$  showed a good correlation with fibrotic change in the left ventricle.  $^{201}\text{Tl}$  perfusion defect patterns have therefore been strongly related with advancement of myocardial fibrosis in patients with DCM. Autopsy findings also support the relationship between the  $^{201}\text{Tl}$  score and myocardial fibrosis.

The redistribution of  $^{201}\text{Tl}$  scintigraphy in patients with DCM is hardly detectable.<sup>1-3</sup> Dunn et al.<sup>1</sup> performed exercise  $^{201}\text{Tl}$  scanning, in which 40% of patients with cardiomyopathy and 67% with coronary artery disease

showed redistribution on a 4-hour scan. In patients with DCM, reversible defects could not be explained by regional differences in coronary blood flow. Thallium uptake by myocardial cells also depends on factors other than coronary blood flow. In cardiomyopathy, the myocardial cell membrane in some areas of the heart may be abnormal, resulting in inhomogeneous uptake of thallium. Reversible defects may also result from the change in left ventricular geometry between the time of the exercise and the redistribution scans. Perfusion defect on thallium imaging can occur in patients with idiopathic dilated cardiomyopathy and chronic heart failure, but it cannot be a definitive index in patients with chronic heart failure to distinguish coronary artery disease from cardiomyopathy even if a complete defect is present. In our study, reversible defects were not evaluated, because the majority of the patients could not perform the exercise test, and the number of subjects was insufficient.

It is difficult to express the area of abnormal uptake with our scoring method, and this method may not necessarily detect the magnitude of abnormal uptake. The interpretation of  $^{201}\text{Tl}$  myocardial SPECT images is a subjective process, and whether it corresponds with the degree of histological fibrosis or not is open to question. In this study, the Bull's eye method has also been used to evaluate defects semiquantitatively in order to obtain a clear answer. These findings showed a high correlation between %  $^{201}\text{Tl}$  uptake, DR, CV% and biopsy of fibrosis with DCM. Thus visual findings were supported by a semiquantitative method in our study. Because the data available in this study were filed over the long period, not all of the studies were possible to evaluate semiquantitatively by the Bull's eye method, but serial studies that were done by the Bull's eye method provided clear results, as shown here.

DCM is a disease characterized by enlargement of the left ventricular cavity and reduction in myocardial contractility. In many DCM patients, the wall motion was diffusely reduced, resulting in a characteristic decrease in left ventricular function,<sup>17-19</sup> unlike old myocardial infarction (OMI), which shows signs of synchrony. No significant correlation was reported to be found between  $^{201}\text{Tl}$  myocardial uptake and left ventricular ejection fraction (LVEF) in patients with DCM.<sup>20</sup> In our study, no correlation was also observed between the defects of resting  $^{201}\text{Tl}$  SPECT and LVEF or LVDd. Our data indicate that dilation of the left ventricle may lead to apical thinning, and apical defects of  $^{201}\text{Tl}$  imaging, but no patchy perfusion defect was detected in patients with aortic valve insufficiency showing similar decreases in LVEF and LVDd with DCM. Our classification by means of  $^{201}\text{Tl}$  images is therefore useful for evaluation and differentiation between DCM and aortic valve insufficiency with low LVEF and/or a large left ventricular cavity.

## STUDY LIMITATIONS

There have been some limitations to this study. The first limitation is that biopsy specimens are taken in a very restricted area of the heart. It is clinically impossible to take samples of the myocardium from all around the ventricle as in a  $^{201}\text{Tl}$  SPECT image. For this reason, direct comparison between  $^{201}\text{Tl}$  findings and those of biopsies may be difficult, but Onodera et al. reported that the percent area of fibrosis in the septum, anterior, lateral and posterior walls of the left ventricle in DCM showed no significant differences among groups.<sup>4</sup> This suggests that biopsy findings may represent to some extent total left ventricular fibrosis, showing that comparison of biopsy specimens with the  $^{201}\text{Tl}$  image is reasonable. Secondly, this study only assessed the correlation between  $^{201}\text{Tl}$  defects and myocardial fibrosis. The possibility of the production of perfusion defects by other factors in patients with DCM, such as metabolic change, should be further evaluated. Thirdly, in the present study, the redistribution image was not assessed, because the number of subjects was insufficient. Redistribution, perhaps related to thallium extraction and viable myocardial muscle, may exist at rest or be induced by exercise, and will produce perfusion defects in the  $^{201}\text{Tl}$  image. The possibility of a different image in the redistribution phase will be less, but further evaluation is necessary to understand the effect of redistribution. Lastly, this retrospective study was performed over a long period, and it is possible that differences in assessing images because of differences in the types of devices used and in image quality.

## CONCLUSIONS

Perfusion defects were observed by  $^{201}\text{Tl}$  myocardial SPECT in 94.6% of the patients with DCM in whom fibrosis was demonstrated by biopsy.  $^{201}\text{Tl}$  myocardial SPECT showed inhomogeneous perfusion defects in many patients (78.4%). The appearance of multiple small defects in myocardial SPECT was in close agreement with histological detection of myocardial fibrosis in DCM. Evaluation by the Bull's eye semi-quantitative method supported these findings. The grading of perfusion defects in  $^{201}\text{Tl}$  myocardial SPECT imaging was also in close agreement with the autopsy findings in endomyocardial fibrosis. The inhomogeneous perfusion defects on the  $^{201}\text{Tl}$  SPECT imaging are therefore considered to be one of the markers of myocardial fibrosis, which is not totally dependent on cardiac function, although further evaluation is needed for more reasonable grading. These results may contribute to the clinical evaluation of DCM or differentiation from other disease. The above grading of perfusion defects on  $^{201}\text{Tl}$  myocardial SPECT imaging may be useful in determining histopathological changes, including fibrosis in patients with DCM.

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