

Thallium Scintigraphy for the Prognosis of Idiopathic Dilated Cardiomyopathy

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Abstract

Objectives. This study evaluated the significance of perfusion defects demonstrated by thallium-201 and age in the prognosis of patients with idiopathic dilated cardiomyopathy.

Methods. Seventy-four dilated cardiomyopathy patients underwent thallium scintigraphy as well as clinical and hemodynamic examination.

Results. Abnormal perfusion defects were present in 23 of 38 patients aged < 60 years (61%) and in 26 of 36 elderly patients aged \geq 60 years (72%; NS). Univariate analysis showed that such perfusion defects were a significant predictor of cardiac death only in patients aged < 60 years ($p = 0.015$). Stepwise discriminant analysis also revealed that perfusion defects were a significant predictor in patients aged < 60 years (Wilks' lambda 0.499, chi-square test 20.2, $p = 0.003$). Perfusion defects were not more important than the history of syncope or stroke in elderly dilated cardiomyopathy patients. Twenty-one patients died of disease-related causes during 58 ± 43 months. The five-year survival rate was better in patients aged < 60 years without than in those with perfusion defects (100% vs 58.4%, respectively) but not affected in patients aged \geq 60 years (66.7% vs 62.2%).

Conclusions. Thallium scintigraphy is valuable for the prognosis of patients with dilated cardiomyopathy aged < 60 years who are usually candidates for heart transplantation. Absence of thallium perfusion defects may indicate good long-term prognosis.

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Key Words

■Cardiomyopathies, dilated ■Prognosis ■Radionuclide imaging (^{201}Tl)

INTRODUCTION

The prognosis for patients with idiopathic dilated cardiomyopathy is poor^{1,2}. The clinical course is usually characterized by progressive deterioration of heart failure complicated by systemic thromboembolism, followed by sudden death¹⁻⁴. Prediction of deterioration in individual patients remains difficult⁴⁻¹³.

Dilated cardiomyopathy is the principal indication for heart transplantation^{14,15}, but this treatment

is available only to a minority of patients because of the small supply of donor hearts, so careful selection of patients is mandatory^{16,17}. This study investigated the use of thallium-201 perfusion defects and age compared to conventional evaluation in patients with dilated cardiomyopathy.

SUBJECTS AND METHODS

Subjects

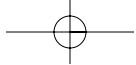
We studied 74 consecutive patients with dilated cardiomyopathy (56 men and 18 women, mean age

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58 ± 10 years) who were referred to Kochi Medical School. A careful history was taken from all patients, and they underwent physical examination, blood test, chest radiography, standard electrocardiography, 24-hour Holter recording, exercise stress test, echocardiography, dipyridamole-stress thallium-201 scintigraphy, and cardiac catheterization, including coronary angiography and biplane left ventriculography. Patients with acute myocarditis, significant coronary artery stenosis, valvular disease or a left ventricular end-diastolic volume below 85 ml/m² were excluded.

The patients were divided into two groups according to age: relatively young patients aged < 60 years (38 patients) and elderly patients aged ≥ 60 years (36 patients), since age ≥ 60 years is in practice one of the contraindications for heart transplantation¹⁷⁾.

Thallium-201 myocardial scintigraphy

Dipyridamole-stress myocardial scintigraphy with planar images was performed in all patients, according to Gould's method^{18,19)}, after infusion of 0.568 mg/kg dipyridamole and walking for 3 min in place. Three mCi (111 MBq) of thallium chloride was injected during exercise, and acquisition of three projection images (anterior, 45° left anterior oblique, 70° left anterior oblique) was begun within 5 min of injection with a gamma camera equipped with a high resolution collimator (Toshiba GCA 401-5). Data were acquired with preset time of 5 min and stored in a computer (Toshiba GMS-55A) for subsequent analysis. Identical delayed images were acquired 3 hr later. Data were analysed with a circumferential profile curve, after smoothing and background subtraction of images²⁰⁾, and findings were interpreted by two observers who were unaware of the angiographic and echocardiographic results. Disagreements were resolved by consensus. Defects were classified as reversible or fixed according to the conventional method²¹⁾. However, since no reversible defects were identified, initial images were evaluated for the size and location of the defects. Then, fixed defects were classified into two groups: no defect or only one defect smaller than one segment, and definite perfusion defects, which included multiple small defects and/or a large defect greater than one segment as defined previously (Fig. 1)¹⁰⁾. Small apical defects may be seen in normal subjects²²⁾ and, if present in isolation, are not considered abnormal. The size of

a segment was defined as the section of the arc of the planar image corresponding to 60° at the apical segment and as that corresponding to 90° at the anterolateral, anteroseptal, septal, inferior, infero-posterior and posterolateral segments¹⁰⁾.

Echocardiography

Echocardiography was performed by one of the authors using a Toshiba SSH-65A, a Toshiba SSH-160A, or an Aloka SSD-710 with 2.5- to 3.75-MHz transducers. M-mode and two-dimensional echocardiographies were performed during initial evaluation. Conventional measurements of left ventricular dimensions and derived indices of function were made according to standard criteria.

Ambulatory Holter recording

All patients underwent 24-hour ambulatory electrocardiographic recording. Nonsustained ventricular tachycardia was defined as ≥ three consecutive ventricular premature complexes at a mean rate of 120 beats/min.

Treadmill exercise test

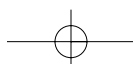
Symptom-limited treadmill exercise testing was performed in the patients not taking cardioactive medications using a modified Bruce protocol. Diagnostic ST segment depression was defined as ≥ 0.1 mV at the J-80 point in at least two leads using standard 12-lead electrocardiography.

Cardiac catheterization

Left heart catheterization and coronary angiography were performed in all patients. Biplane left ventriculography was performed in the 30° right anterior oblique and 60° left anterior oblique projections, and was analysed as described previously. Significant coronary artery stenosis was defined as ≥ 50% reduction of the major coronary arteries.

Follow-up

The mean (± SD) follow-up period was 58 ± 43 months. The clinical outcome was observed in all patients. Current medications at discharge after initial evaluation were diuretics in 71 patients, digitalis in 53, angiotensin converting enzyme inhibitor in 25, beta-blockade in 5, and antiarrhythmic drugs in 39 (mexiletine in 19, disopyramide in 9, others in 11). Deaths were classified as: heart failure, if the patient deteriorated progressively and died with a terminal clinical picture of pulmonary edema or



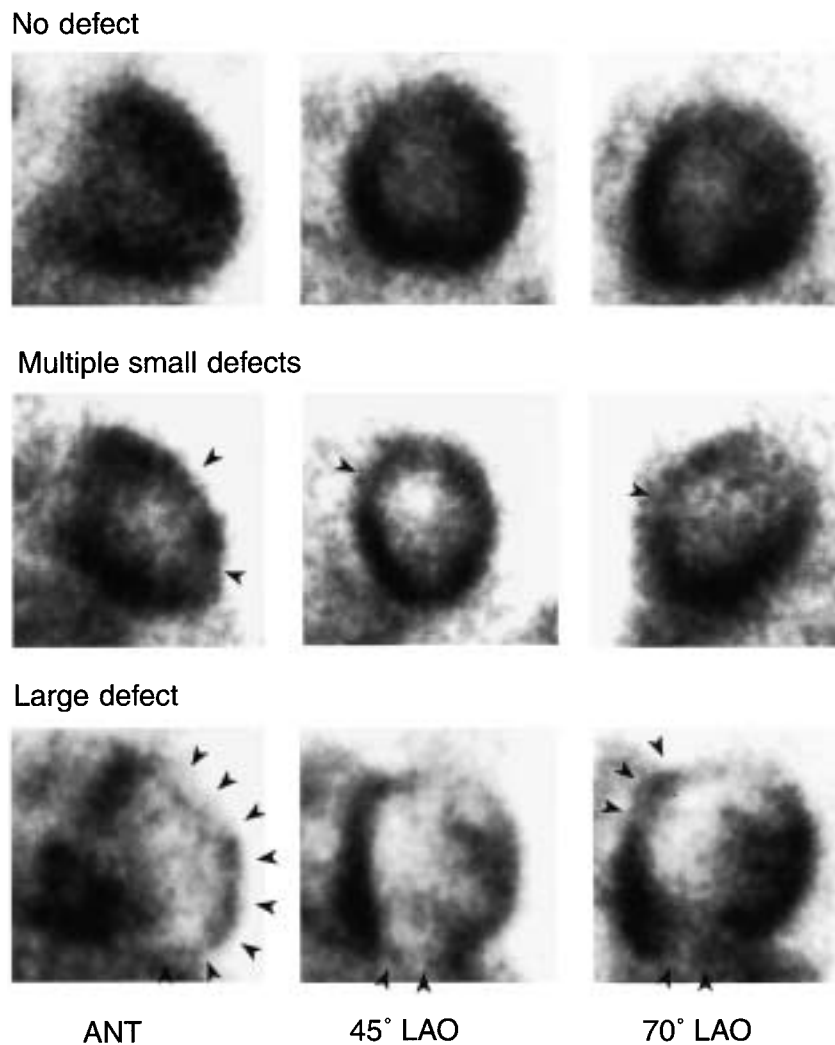


Fig. 1 Representative scintigraphic perfusion defects
 Scintigraphic images showing no defect (upper row), multiple small defects (arrowheads, middle row) and a large defect (arrowheads, lower row).
 ANT = anterior; LAO = left anterior oblique.

cardiogenic shock, or both; sudden, if deterioration and death occurred within 1 hr of the onset of symptoms in a patient with heart failure symptoms that had remained stable or had improved over the previous 2 to 4 weeks; or noncardiac causes.

Statistical analysis

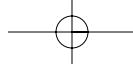
Results are expressed as mean \pm one standard deviation. Student's *t*-test was used to compare the means of continuous variables, and a chi-square test was used for comparison of groups. Survival estimates were obtained by the Kaplan-Meier method. Linear discriminant analysis, with Wilks' lambda as the selection and optimization criterion, was used to assess the potential to predict progno-

sis. The Bayes rule with equal prior probability was used for the predictions, and results are presented as sensitivity, specificity, accuracy and positive predictive value. Statistics were calculated with SPSS-PC + software programs.

RESULTS

Baseline characteristics

Baseline, scintigraphic, echocardiographic, hemodynamic and other characteristics are shown in **Table 1**. There were no significant differences in baseline, scintigraphic and echocardiographic characteristics between the two groups, although the relatively young group aged < 60 years had slightly higher baseline left and right ventricular end-dias-

**Table 1 Basic characteristics**

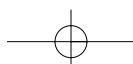
	Age < 60 years (n = 38)	Age ≥ 60 years (n = 36)
Male sex	29(76)	27(75)
Age(yr)	49.9 ± 7.9	66.1 ± 4.9*
Follow-up period(months)	61.3 ± 46.1	54.0 ± 39.0
Cardiothoracic ratio(%)	56.6 ± 5.6	56.2 ± 7.1
NYHA functional class		
-	26(68)	24(67)
-	12(32)	12(33)
Thallium-201 scintigraphy		
Perfusion defect	23(61)	26(72)
Echocardiography		
LVDd(mm)	63.6 ± 6.8	63.3 ± 5.8
LVDs(mm)	55.1 ± 8.4	53.9 ± 7.5
%fractional shortening(%)	13.8 ± 5.5	15.1 ± 5.8
Left atrium(mm)	42.1 ± 6.3	42.4 ± 8.6
Holter ECG		
Ventricular tachycardia	18(47)	10(28)
Atrial fibrillation	8(21)	9(25)
Cardiac catheterization		
LVEDVI(ml/m ²)	150.6 ± 56.8	145.8 ± 36.2
LVESVI(ml/m ²)	104.3 ± 49.8	96.9 ± 27.6
LVEF(%)	33.6 ± 10.5	33.5 ± 10.0
LVEDP(mmHg)	15.6 ± 7.6	11.9 ± 5.4*
PCWP(mmHg)	12.1 ± 7.3	8.9 ± 5.1
RVEDP(mmHg)	8.8 ± 3.5	6.2 ± 2.3*
Cardiac index(ml/min/m ²)	2.3 ± 0.6	2.3 ± 0.7
Treadmill ECG		
Exercise duration(min)	5.9 ± 2.2	4.1 ± 2.1*
BP at peak exercise(mmHg)	39.6 ± 25.5	29.7 ± 20.6
HR at peak exercise(beats/min)	70.0 ± 15.0	57.0 ± 17.8*
Medications		
Diuretics	35(92)	36(100)
Digitalis	28(74)	25(69)
ACE inhibitors	13(34)	12(33)
Beta-blockade	4(11)	1(3)
Antiarrhythmic drugs	20(53)	19(53)

Continuous values are mean ± SD. () %. **p* < 0.05.

NYHA = New York Heart Association; LV = left ventricle; Dd = diastolic dimension; Ds = systolic dimension; ECG = electrocardiography; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; EDP = end-diastolic pressure; PCWP = pulmonary capillary wedge pressure; RV = right ventricle; BP = increase of blood pressure; HR = increase of heart rate; ACE = angiotensin converting enzyme.

tolic pressures, longer exercise duration, and higher increase of heart rate at peak exercise compared with the elderly group aged ≥ 60 years. The incidence of thallium-201 perfusion defects was similar between the two groups(young 61% vs elderly

72%). No reversible defects were observed. The incidence of ventricular tachycardia was also not significantly different between the two groups (young 47% vs elderly 28%).



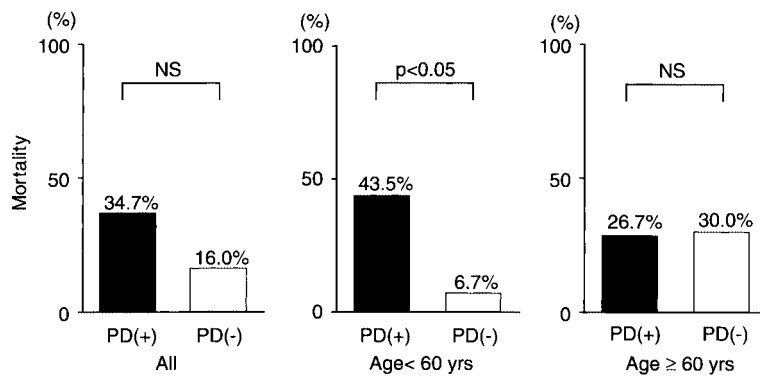


Fig. 2 Comparison of mortality rates between patients with and without scintigraphic perfusion defects
PD = perfusion defect.

Table 2 Univariate analyses

	Age < 60 years			Age ≥ 60 years		
	Survivor (n = 27)	Non-survivor (n = 11)	p value	Survivor (n = 25)	Non-survivor (n = 10)	p value
Scintigraphic PD(%)	48	91	0.015	72	70	NS
NYHA - (%)	78	45] NS	80	40] 0.031
NYHA - (%)	22	55		20	60	
History of syncope(%)	19	55	0.026	4	20	NS
History of stroke(%)	15	27	NS	4	40	0.010
Cardiothoracic ratio(%)	55 ± 5	60 ± 6	0.009	55 ± 7	60 ± 6	NS
Left atrium(mm)	42 ± 6	42 ± 7	NS	41 ± 9	47 ± 6	0.043
Ventricular tachycardia(%)	37	73	0.045	24	40	NS
LVEDVI(ml/m ²)	142 ± 54	174 ± 60	NS	145 ± 36	146 ± 40	NS
LVESVI(ml/m ²)	97 ± 47	124 ± 54	NS	91 ± 24	110 ± 36	NS
LVEF(%)	34 ± 11	31 ± 9	NS	36 ± 9	25 ± 11	0.001
LVEDP(mmHg)	13 ± 6	22 ± 9	0.001	10 ± 5	17 ± 5	0.002
PCWP(mmHg)	11 ± 7	15 ± 9	NS	8 ± 3	13 ± 8	0.016
RVEDP(mmHg)	8 ± 3	10 ± 5	NS	6 ± 2	6 ± 2	NS
Cardiac index(ml/min/m ²)	2.4 ± 0.6	2.0 ± 0.5	NS	2.1 ± 0.6	2.5 ± 0.7	NS

Continuous values are mean ± SD.
Abbreviations as in Table 1, Fig. 2.

Clinical outcome

During the follow-up period of 58 ± 43 months, 21 patients died of disease-related causes: 17 of heart failure, 4 of sudden death(overall mortality rate 28.3%), and 1 patient of noncardiac cause (malignancy).

Comparison of mortality between patients with and without perfusion defects is shown in **Fig. 2**. The young group aged < 60 years had significantly higher mortality rate in those with perfusion defects than in those without perfusion defects(43.5% vs 6.7%, p < 0.05). The elderly group aged ≥ 60 years showed no difference(26.7% vs 30.0%, NS).

Univariate analysis and prognosis (Table 2)

Young group(age < 60 years): Patients who died had a higher incidence of thallium-201 perfusion defect, increased cardiothoracic ratio, history of syncope, ventricular tachycardia and elevated left ventricular end-diastolic pressure, compared with the survivors. The New York Heart Association(NYHA)functional class at initial diagnosis, history of stroke, echocardiographic left atrial dimension, left ventricular ejection fraction and cardiac index were not different in survivors versus non-survivors.

Elderly group(age ≥ 60 years): Patients who died had a higher incidence of severe NYHA functional class at initial diagnosis, history of stroke,

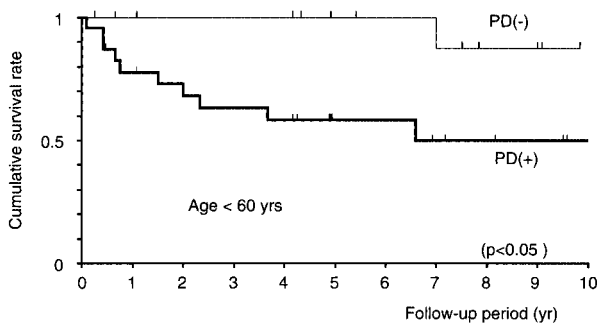
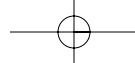


Fig. 3 Survival analysis of patients aged < 60 years, according to the presence or absence of scintigraphic perfusion defects
Abbreviation as in Fig. 2.

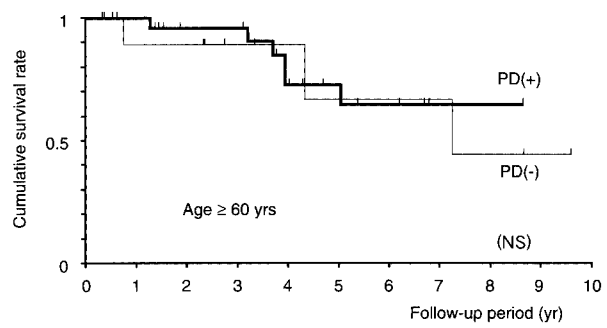


Fig. 4 Survival analysis of patients aged ≥ 60 years, according to the presence or absence of scintigraphic perfusion defects
Abbreviation as in Fig. 2.

enlarged left atrial dimension, elevated left ventricular end-diastolic and pulmonary wedge pressures and low ejection fraction, compared with the survivors. The incidence of perfusion defects and ventricular tachycardia, history of syncope and cardiac index were not different in survivors vs non-survivors.

Multivariate analysis for survival

Apart from scintigraphic perfusion defects, the following 11 variables were considered as potential predictors for cardiac death during the follow-up and were entered into a stepwise discriminant analysis: history of syncope, history of stroke, NYHA functional class, cardiothoracic ratio, echocardiographic left atrial dimension, ventricular tachycardia, left and right ventricular end-diastolic pressures, left ventricular end-systolic volume index, ejection fraction and cardiac index.

Young group(age < 60 years): Multivariate analysis in 38 patients showed a sensitivity of 82%, specificity of 78%, and accuracy of 81% in the prediction of death(Wilks 'lambda 0.549, chi-square test 18.3, $p = 0.003$) Adding the perfusion defect significantly improved the predictability of death (sensitivity 93%, specificity 78%, accuracy 89%) (Wilks 'lambda 0.499, chi-square test 20.2, $p = 0.003$)

Elderly group(age ≥ 60 years): Multivariate analysis in 36 patients showed a sensitivity of 95%, specificity of 100%, and accuracy of 96% in the prediction of death(Wilks 'lambda 0.334, chi-square test 24.7, $p = 0.0009$) Adding the perfusion defect did not improve the predictability of death (sensitivity 95%, specificity 100%, accuracy 96%) (Wilks 'lambda 0.334, chi-square test 24.7, $p =$

0.0009)

Survival analysis

Kaplan-Meier survival estimates were similar between the young(age < 60 years)and the elderly (age ≥ 60 years)groups, with one- and five-year survival estimates of 86.7% and 74.4%, respectively, in the young group, and 97.0% and 64.6%, respectively, in the elderly group.

Young group(age < 60 years): Kaplan-Meier survival estimates according to the absence or presence of the scintigraphic perfusion defects provided one- and five-year survival rates of 100% and 100%, respectively, in patients without perfusion defects, and 77.8% and 58.4% in patients with perfusion defects($p < 0.05$; **Fig. 3**)

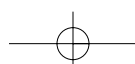
Elderly group(age ≥ 60 years): Survival estimates provided one- and five-year survival rates of 88.9% and 66.7%, respectively, in patients without perfusion defects, and 96.0% and 62.2%, respectively, in patients with perfusion defects(NS ; **Fig. 4**)

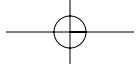
DISCUSSION

The present study showed that perfusion defects by thallium scintigraphy was useful to select patients with dilated cardiomyopathy aged < 60 years who could be candidates for heart transplantation, but was not useful in those aged ≥ 60 years. The absence of thallium perfusion defects also indicated good long-term prognosis in patients aged < 60 years.

Natural history of dilated cardiomyopathy

Although the true natural history of idiopathic dilated cardiomyopathy is difficult to determine





since asymptomatic cardiomegaly may be present for many years, symptomatic patients generally have a poor prognosis^{2,3}. Early studies suggested survival was 70 - 75% at 1 year and approximately 50% at 5 years^{2,9}. More recent studies suggest a better prognosis with a five-year survival rate of 65 - 80%^{3,4}. This change in survival may reflect the earlier detection of the disease and also better treatment. In this study, 21 patients had disease-related mortality during the five-year follow-up, and a survival rate of 70%. There were no significant differences in survival rate at 5 years between the relatively young patients(age < 60 years)and the elderly patients(age ≥ 60 years), although previous reports suggested lower age was one of the clinical features associated with a favourable prognosis^{2,3,10}.

Predictors of adverse outcome

Several clinical, hemodynamic and other features are helpful in assessing the prognosis of patients with dilated cardiomyopathy. Ventricular arrhythmias and thromboembolic complications are both common features of dilated cardiomyopathy, but the prognostic importance of these features remains unclear. The prognosis is most closely related to the severity of left ventricular dysfunction. Clinical features such as syncope, a third heart sound, right-sided heart failure, increased cardiothoracic ratio and left ventricular conduction delays may be associated with a poor prognosis^{2,6,12}. Hemodynamic features such as increased filling pressures, low cardiac index, low ejection fraction, and decreased oxygen consumption are also associated with a poor prognosis^{2-4,9,10}. Although these clinical and hemodynamic features are useful, the assessment of prognosis for individual patients remains difficult.

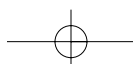
Thallium-201 perfusion defects

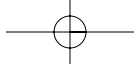
Several patterns of perfusion defects occur in patients with dilated cardiomyopathy^{23,24}. A large fixed defect or multiple small fixed defects, or both, are frequent and associated with impaired cardiac function¹⁰. The extent of perfusion defects is an important prognostic variable, although it was not considered in this study. Reversible defects were not seen in the present study, although they can sometimes be detected in patients with dilated cardiomyopathy. Thus, some small reversible defects may have been overlooked in the present study with planar imaging. Our study must be considered

preliminary because of these limitations. Thallium-201 scintigraphy for the prediction of outcome in patients with dilated cardiomyopathy is not well defined. In clinical practice, age ≥ 60 years is one of the contraindications for heart transplantation. In this study, we divided the patients with dilated cardiomyopathy into young patients aged < 60 years and elderly patients aged ≥ 60 years. Presence of perfusion defects was a significant predictor of cardiac death in the young group in univariate and also multivariate analyses. The statistical significance was similar to the history of syncope and stroke in the elderly group. Five-year survival was better in young patients without perfusion defects than in those with defects. However, five-year survival was not affected by perfusion defects in elderly patients. Thus, we believe that presence and absence of scintigraphic perfusion defects may provide important information for assessing the prognosis of patients with dilated cardiomyopathy.

Heart transplantation

Idiopathic dilated cardiomyopathy remains the principal indication for heart transplantation. However, there are several complications related to heart transplantation such as the risks of rejection, immunosuppression and infection. The limited number of donor hearts is also a major problem¹⁶. In addition, some patients with dilated cardiomyopathy show improvement in left ventricular systolic function^{11,13}, in particular, cases of less than six-months 'duration'⁸. Careful selection of patients is therefore important. Cardiopulmonary exercise testing has been one of the useful preoperative predictors of a favorable outcome after transplantation¹⁵. Age ≥ 60 years has been considered as one of the important and realistic contraindications in clinical practice, so we analysed our data of thallium-201 perfusion defects in 74 patients according to age, for comparison with conventional evaluation. In patients aged < 60 years, presence of thallium perfusion defects was a significant predictor of cardiac death, and five-year survival was better in patients without perfusion defects than in those with defects. This suggests that thallium perfusion defects may be a useful clinical characteristic and is helpful in the selection of patients for transplantation, although sufficient preoperative medical treatment with angiotensin converting enzyme-inhibitors and beta-blockades is mandatory. Absence of defects may indicate that such patients





will respond well to medical therapy.

Study limitations

Study limitations include the retrospective nature, and the variation in medical treatment. In particular, use of angiotensin converting enzyme-inhibitors and beta-blockades remained low in this study, mainly because of the retrospective nature, despite the considerable evidence suggesting the usefulness of these medications in improving the prognosis of dilated cardiomyopathy patients. Second, the number of patients was relatively low and some of the statistical analyses might have been affected. Third, all patients underwent planar imaging. Tomographic imaging with single photon emission computed tomography may improve the resolution and increase the diagnostic value of thallium scintigraphy, particularly in patients with coronary artery disease. However, tomographic

imaging was not available during the period of the study. The extent of perfusion defects was not included in the evaluation, although we believe that whole myocardial information regarding the presence and type of perfusion defects can be obtained with planar imaging in patients with dilated cardiomyopathy. Myocardial biopsies were not performed, although we excluded patients clinically suspected of having secondary myocardial disease or myocarditis.

CONCLUSIONS

Presence of thallium-201 perfusion defects was a valuable indicator of the outcome in patients with dilated cardiomyopathy aged < 60 years, who are usually candidates for heart transplantation. Absence of such perfusion defects indicates good long-term prognosis.

要 約

タリウム心筋シンチグラフィによる特発性拡張型心筋症の予後評価

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松村 敬久 山崎 直仁 土居 義典

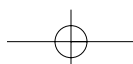
目 的: この研究の目的は特発性拡張型心筋症の予後評価について、タリウム(Tl)心筋シンチグラフィの欠損像の意義を検討することにある。

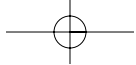
方 法: 74例の拡張型心筋症患者を対象として、Tl心筋シンチグラフィとともに各種臨床検査、血行動態検査を施行して評価した。

結 果: 異常なシンチグラフィ欠損像は、60歳未満の38例中23例(61%)に、また60歳以上の36例中26例(72%)にみられた(有意差なし)。単変量解析では、シンチグラフィ欠損像は、60歳未満の患者においてのみ心臓死の予測因子であった($p = 0.015$)。ステップワイズ判別分析においても、シンチグラフィ欠損像は60歳未満の患者で有意な予測因子であった(Wilks' lambda 0.499, 2 検定 20.2, $p = 0.003$)。一方、60歳以上の高齢群では、シンチグラフィ欠損像の予測因子としての重要性は、失神または脳梗塞の既往と同等であった。平均 58 ± 43 カ月の経過中、21例の疾患関連死がみられた。60歳未満の患者の5年生存率は、シンチグラフィ欠損像を示さない例が欠損像を示す例より良好であった(100% vs 58.4%)。一方、60歳以上の患者の5年生存率は、シンチグラフィ欠損像の有無と相関を示さなかった(66.7% vs 62.2%)。

結 論: 心筋シンチグラフィによる拡張型心筋症の予後評価は、一般的に心移植の適応となる60歳未満の患者においてとくに有用である。シンチグラフィ欠損像が存在しなければ、良好な長期予後が期待できる。

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