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Defect Images in Stress Thallium-201 Myocardial Scintigraphy in Patients With Complete Left Bundle Branch Block: Comparison of Exercise Stress and Pharmacological Stress

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Abstract

Objectives. Stress thallium-201 (^{201}Tl) myocardial scintigraphy can demonstrate perfusion abnormalities, especially in the septum in patients with complete left bundle branch block (CLBBB) even with angiographically normal coronary arteries. Differences in the images between exercise and pharmacological stress ^{201}Tl myocardial scintigraphy were evaluated in patients with CLBBB and normal coronary arteries.

Methods. Forty-five patients with CLBBB underwent exercise stress using treadmill or pharmacological (adenosine triphosphate) stress ^{201}Tl myocardial scintigraphy from October 1997 to February 2003. Patients with myocardial diseases were excluded, such as cardiomyopathy and coronary artery diseases detected by echocardiography and/or cardiac catheterization. The myocardial segment was classified according to the American Heart Association style for coronary artery disease.

Results. Peak blood pressure levels and heart rates were significantly higher in the exercise stress group than in the pharmacological stress group ($p < 0.001$). The rate of defects in stress images was significantly higher in the exercise stress group (72.4%; 21/29 cases) than in the pharmacological stress group (18.8%; 3/16 cases) ($p < 0.01$). The rate of redistribution of observed defects in delayed images was 76.2% (16/21 cases) in the exercise stress group, and 0% (0/3 cases) in the pharmacological stress group ($p < 0.01$). The myocardial segments showing defects were different between the exercise stress group and the pharmacological stress group.

Conclusions. Patients with CLBBB showed different frequencies of defects by stress ^{201}Tl myocardial scintigraphy according to the stress method. Moreover, defects also occured in areas other than the septum. Blood pressure and heart rate were involved in the mechanisms of defects in left bundle branch block.

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Key Words

■ **Heart block (complete left bundle branch block)** ■ **Stress** ■ **Exercise**
■ **Radionuclide imaging (^{201}Tl myocardial scintigraphy)** ■ **Adenosine (ATP)**

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INTRODUCTION

Complete left bundle branch block (CLBBB) is often associated with heart diseases such as coronary artery disease, cardiomyopathy, hypertensive heart disease, and aortic valve disease.[1–4] The Framingham Study reported that more than 40% patients with CLBBB have associated ischemic heart disease.[5] Moreover, assessment of ST-T changes by exercise stress electrocardiography is difficult in the presence of CLBBB, so that stress myocardial perfusion scintigraphy is important in diagnosing ischemic heart disease in patients with CLBBB.

Stress thallium-201 (^{201}Tl) myocardial perfusion scintigraphy is a noninvasive examination with higher sensitivity and specificity than other noninvasive examinations, so is a very useful examination to diagnose coronary artery diseases such as angina pectoris and myocardial infarction.

Stress ^{201}Tl myocardial perfusion scintigraphy can demonstrate perfusion abnormalities, especially in the septum in patients with CLBBB and normal coronary arteries.[6–11] The concealment of sarcoidosis and amyloidosis, as well as microcirculatory disturbances resulting from asynchronous contraction, are considered to be involved in the mechanisms of defects in images on stress ^{201}Tl myocardial perfusion scintigraphy in CLBBB. However, the details of the mechanisms remain unclear.

The present study retrospectively compared the frequencies and the regions of defects in patients with CLBBB and normal echocardiographic and coronary angiographic images by stress ^{201}Tl myocardial perfusion scintigraphy using the exercise stress method and the pharmacological stress method.

SUBJECTS AND METHODS

Subjects

Forty-five patients with CLBBB underwent exercise stress (29 cases) or pharmacological [adenosin triphosphate (ATP)] stress (16 cases) ^{201}Tl myocardial perfusion scintigraphy from October 1997 to February 2003 at the Jikei University Hospital. Patients with heart diseases, including valvular diseases, cardiac hypertrophy, cardiomyopathy, and coronary artery diseases detected by echocardiography and/or cardiac catheterization, and patients treated with digitalis or potassium channel blockers were excluded. All patients were routinely instructed to discontinue all drugs for 24 hr before exercise or pharmacological stress. All patients gave informed written consent.

Exercise stress method

Treadmill exercise stress was performed using the standard Bruce protocol. Blood pressure, heart rate, and 12-lead electrocardiography were monitored during the exercise. At peak exercise, ^{201}Tl tracer was injected intravenously, and exercise was continued for one more minute. We defined the target heart rate as (220−age)/min, and only those patients whose maximum heart rate was 85% or more of the target heart rate during exercise were enrolled in the study.

Pharmacological stress method

Pharmacological stress used adenosine triphophate disodium [ATP: 160 μg/kg/min (0.92 m*l*/kg)] continuously injected intravenously for 5 min. Blood pressure, heart rate, and 12-lead electrocardiography were monitored during the test. After ATP administration, ^{201}Tl tracer was intravenously injected.

Single photon emission computed tomography method

^{201}Tl tracer was used for both exercise stress and pharmacological stress myocardial perfusion scintigraphy. Three mCi of ^{201}Tl was intravenously injected at peak exercise. A single-crystal rotating gamma camera was used to take images 15 min after stress loading (stressed image), and 4 hr after stress loading (delayed image).

Classification of myocardial segments

Myocardial segments were expressed according to the American Heart Association's left ventriculography style for coronary artery disease (**Fig. 1**).[12] In addition, the degree of ^{201}Tl accumulation was determined by two cardiologists and one radiologist, and expressed using a four-step defect scoring system in which 0 = normal, 1 = mild reduction, 2 = severe reduction, and 3 = defect. This defect scoring system was also used for evaluation of the presence or absence of redistribution and reverse redistribution of ^{201}Tl.

Statistical analysis

Differences in characteristics were compared using the χ^2 test or the Student's *t*-test. Differen-

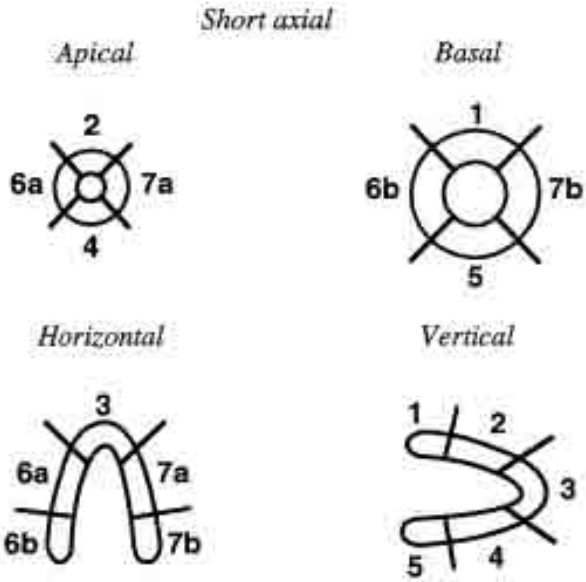

Fig. 1 Myocardial segments according to the American Heart Association's left ventriculography style for coronary artery disease
0 = normal, 1 = mild reduction, 2 = severe reduction, 3 = defect.

ces were considered significant at $p < 0.05$.

RESULTS

Patient characteristics (Table 1)

The exercise stress group included significantly more males than the pharmacological stress group ($p < 0.05$). Height and body weight were significantly greater in the exercise stress group than in the pharmacological stress group ($p < 0.01$). The two groups showed no significant difference in age, body mass index, and presence of coronary risk factors such as smoking, hypertension, diabetes mellitus, hyperlipidemia, and family history of coronary artery diseases.

Heart rate and blood pressure before stress and at peak stress (Table 2)

The two groups showed no significant difference in heart rate or blood pressure before stress. Heart rate, blood pressure, and double products (heart rate × systolic blood pressure) at peak stress were significantly higher in the exercise stress group than in the pharmacological stress group ($p < 0.001$).

Rates of defects in stress images (Table 3)

The rate of defects in stress images was significantly higher in the exercise stress group (72.4%; 21/29 cases) than in the pharmacological stress group (18.8%; 3/16 cases) ($p < 0.01$).

Rates of reverse redistribution in delayed images (subjects showed no defect in stressed images)

Patients who showed no defect in stressed images also showed no reverse redistribution of ^{201}Tl in the delayed images in both groups. There was no significant difference in the rates of reverse redistribution in delayed images between the two groups.

Table 1 Patient characteristics

	Exercise stress group (n=29)	Pharmacological stress group (n =16)	p value
Sex (male/female)	25/4	9/7	<0.05
Age (yr)	61.3 ±11.7	73.7±8.9	NS
Height (cm)	165.6±7.2	155.3±5.4	<0.01
Weight (kg)	63.3±8.8	54.9 ±11.7	<0.01
Body mass index	21.1±2.7	22.6±4.1	NS
Smoking	16(55.2)	4(25.0)	NS
Diabetes mellitus	4(13.8)	6(37.5)	NS
Hypertension	14(48.3)	13(81.3)	NS
Hyperlipidemia	13(44.8)	5(31.3)	NS
Family history of CHD	8(27.6)	2(12.5)	NS

Continuous values are mean±SD. ( ): %.
CHD=coronary heart disease.

Table 2 Heart rate and systolic blood pressure before stress and at peak stress

	Exercise stress group (n=29)	Pharmacological stress group (n=16)	p value
HR before stress (beats/min)	82.7±11.7	75.1±15.9	NS
BP before stress (mmHg)	139.6±19.5	142.1±25.8	NS
HR at peak stress (beats/min)	153.6±15.9	84.2±16.7	<0.001
BP at peak stress (mmHg)	203.8±30.6	122.0±19.3	<0.001
DP at peak stress	31,395±6,374	10,153±2,037	<0.001

Values are mean±SD.
HR=heart rate; BP=systolic blood pressure; DP=double products (HR×BP).

Table 3 Rates of defects in stress images

	Exercise stress group (n=29)	Pharmacological stress group (n=16)	p value
Rates of defects	72.4% (21/29)	18.8% (3/16)	<0.01

Table 4 Rates of redistributions and reverse redistributions in delayed images

	Exercise stress group (n=21)	Pharmacological stress group (n=3)
RD(+)	66.7% (14/21)	0% (0/3)
RD(−)	23.8% (5/21)	100% (3/3)
Reverse RD(+)	9.5% (2/21)	0% (0/3)

Subjects showed defects in stress images by each stress method.
RD=redistributions.

Table 5 Myocardial segments showing defects in stress images

Segments	Exercise stress group (n=21)	Pharmacological stress group (n=3)
1	47.6% (10/21)	33.3% (1/3)
2	42.9% (9/21)	66.7% (2/3)
3	33.3% (7/21)	66.7% (2/3)
4	38.1% (8/21)	33.3% (1/3)
5	42.9% (9/21)	0% (0/3)
6a, 6b	81.0% (17/21)	33.3% (1/3)
7a, 7b	0% (0/21)	33.3% (1/3)

Segments were expressed according to the American Heart Association's left ventriculography style for coronary artery disease.

Rates of redistribution and reverse redistribution in delayed images (subjects showed defects in stressed images) (Table 4)

The rates of redistribution in delayed images were 66.7% in the exercise stress group and 0% in the pharmacological stress group. The rates of reverse redistribution were 9.5% in the exercise stress group and 0% in the pharmacological stress group. There was a significant difference between the two groups ($p < 0.05$). Although two-thirds of the patients in the exercise stress group showed redistribution, neither redistribution nor reverse redistribution were seen in the pharmacological stress group.

Myocardial segments showing defects in stress images (Table 5)

The myocardial segments showing defects were segments 6 > 1 > 2, and 5 in the exercise stress group, and segments 2, 3 > 1, 4, 6, 7 in the pharmacological stress group. There was no significant difference between the two groups in the myocardial segments showing defects.

DISCUSSION

Stress ^{201}Tl myocardial perfusion scintigraphy is useful to diagnose the presence, location, and severity of coronary artery disease. Stress can be loaded by exercise using a bicycle or a treadmill, or by intravenously injecting drugs such as adenosine, ATP, dipyridamole, and dobutamine. This study performed the exercise method using both the treadmill method and the pharmacological method using ATP.

In stress ^{201}Tl myocardial perfusion scintigraphy, stress loading causes relative increases in the myocardial blood flow in normal coronary arteries, but not in the ischemic regions. Therefore, the tracer uptake carried to the myocardium becomes heterogeneous, and the variance in the distribution can

be seen in the myocardial perfusion image in patients with coronary artery disease. Stress ^{201}Tl myocardial perfusion scintigraphy can demonstrate perfusion abnormalities especially in the septum in patients with CLBBB even whose coronary arteries were angiographically normal. [6–11]

In this study, the rate of defects in stress images was significantly higher in the exercise stress group than in the pharmacological stress group. This study included patients with normal coronary arteries without myocardial diseases. Therefore, the specificities of stress myocardial perfusion scintigraphy were 27.6% for exercise stress scintigraphy and 81.2% for pharmacological stress scintigraphy. The specificities were previously reported as 13–89% for exercise stress scintigraphy and 53–89% for pharmacological stress scintigraphy.[13–18] Moreover, the delayed images in the pharmacological stress group showed no redistribution or reverse redistribution of ^{201}Tl. In the exercise stress group, redistribution was observed in 66.7% and reverse redistribution in 9.5%. These differences in reverse redistribution between exercise and pharmacological stress on ^{201}Tl myocardial scintigraphy suggest that exercise stress and pharmacological stress have different mechanisms for the defects in images.

Currently proposed mechanisms that produce false-positive defect images in patients with CLBBB and normal coronary arteries include true decrease in perfusion (ischemia) and normal perfusion with apparent decrease.[19] The true decrease in perfusion is caused by (i) decreased blood flow in response to lower septal resting oxygen demand (autoregulation), (ii) diastolic compression of septal perforators secondary to abnormal and delayed septal contraction/relaxation, (iii) septal microvessel compression secondary to abnormal and delayed septal contraction/relaxation and redistribution of circumferential shortening, (iv) reduced septal endothelial function and coronary flow reserve, (v) reduced diastolic blood flow due to shorter diastolic filling time, and (vi) cardiomyopathic changes resulting in septal thinning and fiber loss. The normal perfusion with apparent decrease is caused by the partial-volume effect due to decreased septal wall thickness and failure to thicken normally relative to the other walls. Right ventricular electric pacing showed that left bundle branch bloock (LBBB) reduced myocardial perfusion and glucose uptake in the septum[20] and suppression of the K^+ channel.[21]

In this study, heart rate and blood pressure at peak stress were significantly higher in the exercise stress group than in the pharmacological stress group ($p < 0.001$). Blood pressure and left ventricular pressure affect septal microvessel compression and heart rate affects reduced diastolic blood flow. Therefore, exercise stress increases left ventricular pressure and heart rate, and augments septal microvessel compression and reduced diastolic blood flow on asynchronous contraction in CLBBB. However, defects in images without redistribution were observed in the pharmacological stress group, although blood pressure and heart rate were not changed. These results suggest that the myocardium in LBBB might have decreased blood flow caused by autoregulation, reduced septal endothelial function and coronary flow reserve, and cardiomyopathic changes.

In this study, the segments showing defects in stress images were 6 > 1 > 2, and 5 in the exercise stress group, and 2, 3 > 1, 4, 6, and 7 in the pharmacological stress group. Such defects in images have never been found in segments other than the septum in patients with LBBB on stress ^{201}Tl myocardial scintigraphy. Defects in images were found in the septum and almost all the segments. These results suggest that the mechanisms of defects in images may also affect segments other than the septum.

According to the guidelines,[22,23] pharmacological stress is recommended for patients with CLBBB, and the defects in images can predict the prognosis of patients. In our hospital, exercise stress scintigraphy has not been performed for patients with CLBBB since February 2003. This study evaluated patients with normal coronary angiography and echocardiography, so concealed microcirculatory disorder or myocardial disorder at cellular levels cannot be ruled out. Therefore, we should carefully follow up all patients with LBBB.

This study has the limitation of patient characteristics because it is an observational study and retrospective evaluation of our clinical experience with stress ^{201}Tl myocardial scintigraphy in patients with CLBBB.

CONCLUSIONS

The frequencies of defects and redistribution detected by stress ^{201}Tl myocardial perfusion scintigraphy in patients with CLBBB are different using exercise stress and pharmacological stress. The mechanisms of defects in images may involve

heart rate and blood pressure. We should carefully interpret segments other than the septum on stress ^{201}Tl myocardial perfusion scintigraphy in patients with LBBB.

要　約

完全左脚ブロック患者における負荷タリウム-201心筋シンチグラフィーの欠損像: 運動負荷と薬物負荷の比較

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目　的: 完全左脚ブロックでは，冠動脈造影が正常であるのに運動負荷^{201}Tl心筋シンチグラフィー上，とくに中隔において欠損像を呈することがある．しかしながら，そのメカニズムについてはいまだ不明な点が多い．本研究では，負荷方法による欠損像の違いについて検討した．

方　法: 1997年10月−2003年2月に当院において運動または薬物（アデノシン三リン酸）負荷^{201}Tl心筋シンチグラフィーを施行した完全左脚ブロックの患者45例を対象とした．ただし，心エコー図検査および心臓カテーテル検査により心筋症などの心筋疾患および冠動脈疾患を有する患者は除外した．心筋セグメントの表現はAmerican Heart Associationの冠動脈疾患左室造影報告書様式に準じた．

結　果: 負荷時の血圧，心拍数は，薬物負荷に比べ運動負荷で有意に高値を示した（$p < 0.001$）．負荷時に欠損像を認めたのは，運動負荷72.4%（21/29），薬物負荷18.8%（3/16）で，運動負荷で有意に多かった（$p < 0.01$）．そのうち，負荷4時間後において再分布を認めたのは，運動負荷76.2%（16/21），薬物負荷0%（0/3）で，運動負荷で有意に多かった（$p < 0.01$）．欠損像を認めた心筋セグメントは，運動負荷直後ではセグメント 6＞1＞2, 5の順で多かったのに対し，薬物負荷直後ではセグメント2＞1, 3, 4, 6の順で多かった．

結　論: 完全左脚ブロック患者の負荷^{201}Tl心筋シンチグラフィーにおいて欠損像を認める頻度は負荷方法により異なる．欠損像を呈するメカニズムには，血圧，心拍数が関与する．また，中隔以外の部位においても欠損像を呈することがある．

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