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Variations in The Size of The Ischemic Myocardium Due to Differences in The Normal File

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= 국문 초록 =

*Normal File*의 차이에 따른 심근 관류결손 크기의 변화

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혈관확장제 투여에 의한 약물부하 심근스캔시는 운동부하 심근스캔시와 비교하여 심박출량과 관상동맥 혈류의 증가정도가 달라서 심근내 Tl-201의 농도가 달라진다. 그러므로 부하 심근관류스캔의 정량적 판독시에 각각의 부하에 특이적인 Normal file을 사용하지 않으면 이러한 심근내 Tl-201 농도의 차이로 인하여 관류 결손의 크기가 다르게 나타날 수 있으리라 추측할 수 있다. 본 연구는 좌전하행지의 유의한 협착이 있는 34명의 단일 혈관 관상동맥 환자에서 이러한 가정이 실제적으로 어떻게 나타나는가를 조사하였다.

환자들은 adenosine 140 ug/kg/min을 정맥주사하고 Tl-201 SPECT를 실시하였다. 관류결손의 크기는 답차운동부하 Tl-201 스캔을 실시한 정상인에서 구한 Normal File (File-ex)과 adenosine Tl-201 스캔의 Normal File (File-ad)을 각각 이용하여 만든 극성지도에서 구한 adenosine 심근스캔의 관류결손의 범위지수(extent score)와 중증도지수(severity score)로 표시하였고, 이들의 값을 비교하여 아래의 결과를 얻었다. File-ex로 구한 관류결손의 범위지수는 19±13%였고 File-ad로 구한 범위는 11±10%였다(차이 8.1±1.6%, $p=0.0001$). 중증도지수는 File-ex를 사용하였을때 582±479였고 File-ad를 사용하였을때는 310±309였다(차이 272±49, $p<0.0001$). 50~70%의 중등도의 내경 협착이 있었던 20명의 환자에서는 범위지수는 File-ex와 File-ad에서 각각 17±10과 7±7%($p=0.001$)였고, 70% 이상의 내경 협착이 있었던 14명에서의 범위 지수는 각각 24±16과 18±10%($p=0.03$)로 모두에서 File-ex를 사용하였을때의 값이 컸다.

이와 같은 성적으로 보아 Tl-201 스캔에서 관류결손의 정도를 정량적으로 평가할 시에는 부하에 특이적인 Normal File을 사용하여야 관류 결손의 정도를 정확하게 추출할 수 있다는 사실을 알 수가 있다. 즉 dipyridamole이나 adenosine 부하검사에서 운동부하의 Normal File을 사용하면 관류결손의 정도가 과대평가 된다는 것이다.

INTRODUCTION

Patients incapable of exercise because of orthopedic, neurologic or peripheral vascular disease can be evaluated effectively for the presence of significant coronary disease, with the use of pharmacologic agents that produce coronary vasodilation. Extensive clinical experience has shown that dipyridamole-thallium imaging procedure is relatively safe and provides diagnostic and prognostic information from exercise thallium imaging[1~3].

Dipyridamole thallium imaging has proved its clinical usefulness and safety, but prolonged effect poses a potential problem in patients who experience adverse reaction[4,5]. Intravenous infusion of adenosine has been proposed a means of achieving coronary vasodilation directly. Several recent reports[6,10] suggested that adenosine-thallium scintigraphy is a feasible, safe and accurate technique for the detection of coronary artery disease. The increase in the ratio of coronary blood flow to cardiac output with adenosine is known to be greater when compared with exercise[11~12]. Therefore, the myocardial thallium concentration may be different during adenosine stress than exercise testing due to differences in coronary blood flow and cardiac output. These differences may affect the quantitative measurement of the size of the ischemic myocardium if a stress-specific normal file is not used.

This study was designed to examine this concept in 34 paients with isolated left anterior descending coronary artery disease. We examined quantitative measurements (extent and severity score) of perfusion defects during adenosine-thallium imaging using both exercise normal file and adenosine normal file.

METHODS

1. Study Patients

The 34 patients underwent diagnostic cardiac catheterization and coronary angiography for suspected coronary artery disease at Philadelphia Heart Institute were included in this study. All were diagnosed having isolated left anterior descending artery (LAD) disease (≥50% diameter stenosis by coronary angiography). None had Q-wave myocardial infarction on ECG, greater than first degree atrioventricular block, asthma or chronic obstructive pulmonary disease and none were taking theophylline containing medications. There were 16 men and 18 women. All patients underwent intravenous adenosine thallium-201 imaging within 3 weeks of arteriography and antianginal therapy remained unchanged between the studies (Table 1).

2. Coronary Angiography

Coronary angiography was performed in multiple projections using standard techniques. Significant coronary artery disease was defined as more than 50% diameter stenosis in any of the major coronary artery.

3. Adenosine Protocol

Antianginal medications were withheld only on the morning of the test. Patients were studied in the fasting state in the supine position. Intravenous adenosine (Adenoscan™, Medco Research Inc., Los Angeles, California) was initiated at a dose of 0.14 mg/min/kg body weight using an infusion pump and

Table 1. Study Population (n=34)

All patients had isolated LAD disease (≥50% diameter stenosis)	
None had Q-wave myocardial infarction in ECG	
Men/Women :	16/18
Age (years) :	61 ± 10
Hypertension :	17 (50%)
Diabetes mellitus :	2 (6%)
Medications	
nitrates :	17 (50%)
β–blocker :	15 (44%)
calcium channel blocker :	24 (71%)

continued for a total of 6 minutes. At the end of the third minute of infusion, a dose of 3.5 mCi thallium-201 was injected intravenously. Thallium images were obtained 5 minute and 4 hours after thallium injection.

4. Single Photon Emission Computed Tomography (SPECT) Imaging with Thallium-201

Our method for SPECT thallium studies have previously been described[8]. Images are acquired using a circular orbit over 180° arc starting at the 45° right anterior oblique projection and ending at left posterior oblique projection. Each of 32 projections are acquired using a 64×64 matrix at 40 seconds/image. Each projection is corrected for nonuniformity using a 30 million count Co-57 flood.

Standard filtered back projection technique is applied using a Ramp-Hanning filter with a cutoff frequency of 0.83 cycles/cm to generate transaxial slices. No scatter or attenuation correction is used.

Maximal counts circumferential profiles are generated on each of the short-axis slices in forty 9° arcs are ranging from apex to base. These count profiles are then interpolated to the equivalent of 15 slices and stored in two 15×40 arrays, 1 for the stress and 1 for the delayed distribution. For display purposes, these arrays are then transformed into polar plot known as the "raw bull's-eye map". In order to identify stress perfusion defect objectively each patient's profiles are compared to gender matched normal files of adenosine and exercise stress thallium image developed from the low likelihood of coronary artery disease. Previously, it was established that profile curves representing 2.5 standard deviations below the mean normal values as the threshold for stress perfusion defect detection[13]. The cluster profile points falling below this established normal limit are identified as the extent of the defect. Subsequently, these abnormal points are transformed to polar coordinates and plotted in a blackout bull's-eye in which the black region within the bull's eye plot defines the extent of the stress perfusion abnormality. The extent of the perfusion abnormality is estimated as the percentage of the total area and the severity score was derived from

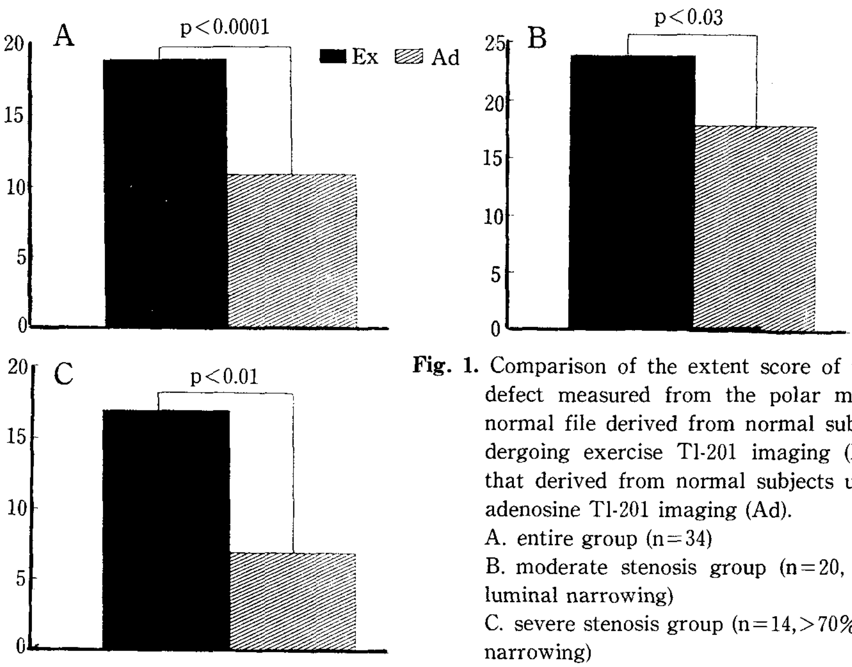

Fig. 1. Comparison of the extent score of perfusion defect measured from the polar map using normal file derived from normal subjects undergoing exercise Tl-201 imaging (Ex) with that derived from normal subjects udergoing adenosine Tl-201 imaging (Ad).
A. entire group (n=34)
B. moderate stenosis group (n=20, 50~70% luminal narrowing)
C. severe stenosis group (n=14,>70% luminal narrowing)

the extent and the number of standard deviations below the mean normal for each point within the abnormal area.

5. Statistical Analysis

Data are represented as mean ± standard deviation (SD) when appropriate. The 95% confidence intervals were used when indicated. Chi-square analysis and Student's t test were used for comparison. A p value of < 0.05 was considered statistically significant.

RESULTS

1. Hemodynamic Responses and Adverse Effects of Adenosine

The heart rate increased from a mean of 68±12 beats/min at baseline to 87±18 beats/min at peak infusion ($p<0.001$). There were no significant changes in diastolic and systolic blood pressures. There was a slight but significant increase in double product during adenosine infusion.

Adverse effects were seen in most of patients but were mostly mild and transient in nature headache, flushing, dizziness and dyspnea. No patient had prolonged chest pain but 7 patients developed ST depression on ECG. In 2 patients, transient second degree atrioventricular block appeared (Table 2).

2. Results of Adenosine SPECT Thallium-201 Images

The overall results are listed in Table 3. The images were abnormal in 28 of the 34 patients with single LAD disease. Twenty-four patients had reversible perfusion defect in LAD vascular territory. Increased lung thallium uptake was noted in 1 patient and 7 patients revealed left ventricular dilation.

Table 2. Side Effects of Adenosine (n=34)

1. Cardiac	
dyspnea	10 (29%)
chest pain	20 (59%)
ST depression > 1 mm	7 (21%)
second degree AV block	2 (6%)
2. Non-cardiac	
headache	9 (26%)
flushing	21 (62%)
nausea	8 (24%)
dizziness	3 (9%)

Table 3. Results of Adenosine Thallium Imaging

Abnormal images :	28 (82%)
Reversible abnormality :	24 (71%)
Increased lung thallium uptake :	1 (3%)
Cavity dilation :	7 (21%)

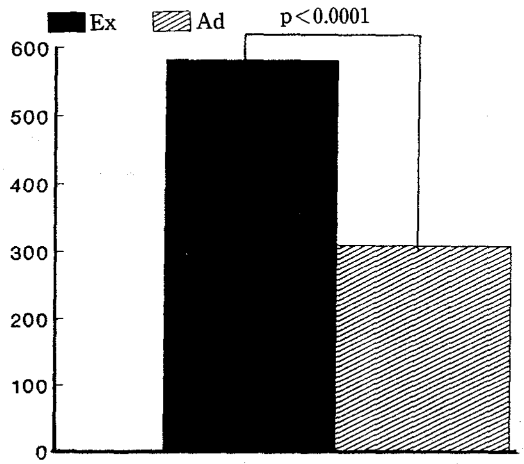

Fig. 2. Comparison of the severity score of perfusion defect measued from the polar map using normal file derived from normal subjects undergoing exercise Tl-201 imaging (Ex) with that derived from normal subjects undergoing adenosine Tl-201 imaging (Ad).

3. Comparison of the Size of the Perfusion Defect Due to Differences in the Normal File

The size of the ischemic myocardium was measured from the polar map using two different normal files; one derived from normal subjects undergoing treadmill exercising test (File-ex) and the second from normal subjects undergoing adenosine stress testing (File-ad).

The extent and severity score during adenosine thallium SPECT were 5.6±5.3% and 125±126 in normal subjects, respectively. The extent of perfusion abnormality was 19±13% using File-ex and 11±10% using File-ad (difference 8.1±1.6%, $p=0.0001$). The severity score was 582±479 using the File-ex and 310±309 using the File-ad (difference 272±49, $p<0.001$). The significant differences in the extent scores were present in the 20 patients with moderate stenosis (50~70% diameter stenosis); 17±10 using File-ex versus 7±7 using File-ad ($p=0.03$), and 14 patients with severe stenosis (more than 70% diameter stenosis); 24±16 versus 18±10 ($p=0.001$).

DISCUSSION

1. Adenosine Thallium-201 Imaging for the Detection of Coronary Artery Disease

Exercise stress thallium-201 scintigraphy is now routinely used for assessing myocardial ischemia. An abnormal perfusion image could be obtained only if the level of exercise stress is sufficient to produce an abnormal distribution of myocardial blood flow[14,15]. Pharmacologic intervention is of obvious value when dynamic exercise yields an inadequate end point for clinical purpose. Perfusion defect during pharmacologic vasodilation are produced by a heterogeneity in coronary blood flow, which is dependent on severity of coronary stenosis and consequent abnormalities in flow[16~18]. Dipyridamole has been used as a safe and effective agent for production of coronary vasodilation for diagnostic testing.

Recently, adenosine infusion has been introduced as an attractive alternative for dipyridamole in combination with thallium-201 imaging, because of its fast onset of action, near maximal coronary vasodilation and less serious side effects due to its short half-life[6~10,19].

Iskandrian et al[8] observed a sensitivity of 92% in a group of 132 patients with documented coronary artery disease and a specificity of 88% among 16 patients without angiographic coronary disease. The adverse effects of adenosine were comparable to those of dipyridamole, except that they are more short-lived and rarely required reversal with aminophylline. Two large multicenter studies[20~22] comparing adenosine with exercise Tl-201 SPECT additionally confirmed the safety of adenosine imaging and demonstrated a high degree of diagnostic agreement between these two modalities.

2. Thallium Kinetics During Stress Thallium Scan

The use of thallium for measuring myocardial blood flow is based on the indicator fractionation principle described by Sapirstein[22]. According to this principle, the fractional uptake of injected tracer by an organ equals the fraction of cardiac output perfusing that organ during the measurement. Merlin et al[23] indicated that under different flow and metabolic conditions, the early fractional uptake of thallium by the left ventricle is a reasonably good approximation of myocardial blood flow as a fraction of cardiac output. Under normal exercise conditions, regional myocardial uptake of thallium is linearly related to the regional coronary perfusion that is proportional to the achieved level of exercise[24,25]. After intravenous injection of thallium with the patients at rest, approximately 3.5 percent of the injected dose localizes in the myocardium: after injection during large muscle exercise, approximately 4.4 percent of the injected dose localizes in the myocardium. Exercise diminishes the activity within the gastrointestinal tract by shunting of splanchnic blood to exercising muscle, besides increased myocardial uptake. After initial uptake of thallium by the myocardium, there begins a slow process of washout of thallium from the myocardial intracellular compartment back into the vascular compartment, and simultaneous representation of additional thallium to the myocardial cells for extraction. The large reservoir of extracardiac thallium initially held by provides a means for equilibrium between the washing out and the reextraction of thallium. The washing out component of the thallium kinetics is also dependent upon coronary perfusion with ischemic areas demonstrating much slower washout than normal regions.

There are some differences in the thallium kinetics between pharmacologic vasodilation and exercise stress testing[26]. There is a great increase in coronary blood flow following a coronary vasodilator compared with exercise. Vasodilator decreases not only coronary but also systemic vascular resistance. This results in increased thallium uptake in tracer-avid organs other than heart, including liver. Bull et al[27] calculated that skeletal muscle takes up two-thirds of the thallium dose injected at peak exercise. In contrast, after dipyridamole, the extracardiac uptake of thallium occurred primarily by the smaller tissue masses of the liver, spleen and splanchnic circulation. Ruddy et al[28] reported that absolute myocardial thallium uptake in normal volunteers was greater after dipyridamole compared with exercise. Furthermore, in their series, blood thallium level, thallium uptake and clearance in the liver, splanchnic region and spleen were greater after dipyridamole.

3. The Size of the Ischemic Myocardium Due to Differences in the Normal File

The regional difference in perfusion is reported to be underestimated by current scintigraphic methods because of overlap of normal and ischemic myocardium, inhomogenous background, tissue attenuation, and subject and cardiac motion[29,30]. The size of the ischemic myocardium during adenosine thallium SPECT measured from the polar map using normal file derived from normal subjects undergoing treadmill exercise was larger compared with that dervied from normal subjects undergoing adenosine stress thallium testing in our study. This result may reflect several different effects of the stress method on depicting perfusion defect during stress thallium imaging.

First, the ratio of coronary blood flow to cardiac output, appears to be most important factor, is larger during adenosine-induced coronary hyperemia than after exercise. The increase in coronary blood flow with adenosine is three times baseline value compatible to that of dipyridamole ranges from 2.4 to 5 times baseline value[31], wheres the increase at exercise is 1.7 to 2.5 times baseline value[32]. This may remarkably increase myocardial blood flow that served by normal vessel and, as a result, increase contrast between normal and ischemic myocardium in myocardial perfusion imaging. Siffring et al[33] showed the mean absolute myocardial thallium uptake was 1.3 times greater with adenosine than with exercise stress testing in normal subjects. The greater achieved myocardial hyperemia and thallium uptake of the myocardium served by normal coronary artery during pharmacologic vasodilation provides adenosine thallium scintigraphy more sensitive than exercise for the quantitation of perfusion defects at the margin of significance. Albro et al[34] demonstrated dipyridamole stress appears to be more sensitive than exercise thallium scintigraphy for localization of coronary stenoses in the 40% to 60% range.

Second, extraction fraction affecting myocardial thallium uptake is different. Increases in coronary flow in excess of myocardial demands, due to pharmacologic vasodilation with adenosine, result in a progressive decrease in thallium extraction[35]. One study[24] suggested that the extraction fraction of thallium decreases to a greater degree with hyperemia due to increased cardiac work. Even there is no general consensus about this concept, it could be supposed that it may affect the quantitation of the size of the perfusion defect.

Third, blood levels of thallium are higher after pharmacologic vasodilation. It is known that blood levels of thallium are higher after dipyridamole, and coronary hyperemia after dipyridamole persists longer than it does after exercise. Therefore the heart is exposured to more thallium after dipyridamole, and this may contribute to the greater myocardial uptake of thallium and could alter the result of quantitative measurement of perfusion defect when stress specific file is not used. The higher blood levels of thallium after dipyridamole decrease the concentration gradient between myocardium and blood, and result in decreased myocardial clearance[25,36]. But this is not clear in case of adenosine stress due to short half life of adenosine.

Fourth, extra-cardiac uptake of thallium is greater, including liver, with adenosine than exercise testing. Since liver lies immediately below the inferior wall of the left ventricle, Compton scatter from the liver and even actual overlap of the superior portion of the liver and the inferior wall of the left ventricle may influence results of quantitative assessment of myocardial thallium uptake[27]. This may affect quantitation of the perfusion defects during adenosine thallium imaging, when stress specific is not used. A recent report[37] suggested that the addition of exercise to pharmacologic vasodilation results in less thallium liver uptake and improved image quality, since exercise results in shunting of blood away from the abdominal viscera to the working musculature.

Another factor should be considered is nonresponder to pharmacologic vasodilator. Rossen et al[4] demonstrated that 2 of 12 patients (17%) in whom coronary blood flow reserve associated with dipyridamle infusion was measured achieved peak flow rate of less than 2.0 ml/min/gm, compared to 3.7± 1.2 ml/min/gm in the entire group. Though the results are not necessarily transferable to patients with adenosine stress imaging, more heterogenous increase in coronary blood flow could occur with pharamacologic vasodilation compared with exercise testing. This may change the size of perfusion defect in patients with adenosine thallium imaging.

4. Clinical Implications

The sensitivity and specificity of adenosine thallium SPECT has been reported to be comparable to those of exercise thallium SPECT[6~10,38,39]. The normal pattern of thallium uptake after adenosine-induced hyperemia differs from that after exercise stress, because achieved myocardial hyperemia and consequent uptake of thallium are greater after adenosine stress than exercise. As a result, quantitative normal limits specific for adenosine-induced hyperemia may be different from that after exercise. The use of exercise file overestimates defect size in patients undergoing pharmacologic stress testing. Thus stress-specific normal file should be used for sizing the perfusion abnormality.

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