# Myocardial Uptake and Clearance of Thallium-201 in Normal Subjects: A Comparison Between Pharmacologic Stress with Intravenous Adenosine, Dipyridamole and Dobutamine, and Exercise Stress Testing

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= 국문 초록 =

## 정상인 심근의 Thallium-201 섭취 및 제거 : Adenosine, Dipyridamole Dobutamine 정맥주사와 운동부하시의 비교

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**정 진 홍**

심근관류 스캔에서 약제부하 검사에 많이 이용되는 것으로는 adenosine, dipyridamole, dobutamine등이 있다. 이 약제들이 혈역학 및 thallium의 약동학에 미치는 효과를 검사하기 위하여 저자들은 15명의 건강인을 대상으로 이들 약제를 정맥주사한 후에와 그리고 운동부하를 시행한 후에 thallium-201 신근관류 스캔을 시행하여 thallium의 약동학에 미치는 영향에 대하여 서로 비교하였다.

부작용은 adenosine(87%), dipyridamole(80%), dobutamine(73%)을 정맥주사할 시에 흔히 나타났으나 경미하였다. 1예에서는 dobutamine을 주사할때의 부작용으로 인하여 최대용량을 투여하지는 못한바 있었다. 대상들은 dipyridamole(13%)이나 dobutamine(27%)보다 adenosine(60%)을 선호하였다($P<0.05$). Thallium의 절대적인 심근섭취는 운동부하 검사보다 adenosine(1.3배), dipyridamole(1.2배), dobutamine(1.4배)부하시에 더 많았고, 이들 약제 사이에는 유의한 차이는 없었다. Thallium의 심근제거율(%/hr)는 운동부하 검사보다 약제부하한 후에가 더 늦었다. 폐, 간, 비장, 및 내장지역에서 thallium의 섭취 및 제거는 운동부하 검사보다 약제부하시에 더 많았으나, 이들 약제 사이에는 유의한 차이가 없었다. Dobutamine투여시의 thallium의 섭취 및 제거는 adenosine 또는 dipyridamole을 투여시의 결과와 상응하였다.

이 논문은 1992년 교육부지원 학술진흥재단의 지방대학육성과제 학술연구 조성비에 의하여 연구 되었음.

저자들은 adenosine, dipyridamole 및 dobutamine을 이용한 약제부하 thallium-201 심근관류 검사를 시행하는데 모든 대상들에서 어려움없이 쉽게 시행할 수 있었다. Thallium의 심근내 섭취 및 제거는 각 약제부하에 따라서 다를 수가 있으므로 심근관류 스캔의 정량적인 분석을 시행할 때는 각각 약제에 대한 특별한 진단기준이 마련되어야 할 것으로 생각된다.

**주요 단어** : Thallium kinetics, Adenosine, Dipyridamole, Dobutamine

## INTRODUCTION

Exercise thallium imaging has been widely used in the diagnosis of coronary artery disease and risk stratification. Patients limited by peripheral vascular, cerebrovascular, neuromuscular, pulmonary, or other systemic or emotional conditions may be unable to achieve a maximal predicted heart rate sufficient to adequate test their coronary flow reserve. Pharmacologic stress testing has been evaluated for many years as an alternative to dynamic exercise test in the assessment of coronary artery disease, especially in patients who are unable to perform adequate exercise. Several drugs have been used for pharmacologic stress testing with myocardial perfusion imaging. The most popular agents are selective coronary vasodilator, such as dipyridamole, adenosine, and cardiac inotropic agent like dobutamine[1~9].

Extensive studies have demonstrated that the diagnostic accuracy of dipyridamole thallium imaging is equivalent to that of exercise thallium imaging[3,4,10]. The mechanism of dipyridamole induced coronary vasodilation is increased blood level of adenosine due to decreased cellular reuptake metabolism[11]. Although dipyridamole thallium imaging has proved its clinical usefulness and safty, its prolonged use posses a potential problem in patients who experience adverse reaction[12]. Moreover, dipyridamole does not elicit in a substantial number of patient receiving usual dose(0.14/kg/min). Adenosine is another powerful coronary vasodilator with short half life. Recently, adenosine infusion has been introduced as an attractive alternative for dipyridamole, because of its fast onset of action, near maximal coronary vasodilation and less serious side effects[5,6,13]. The sensitivity and specificity of adenosine thallium imaging were comparable to those of exercise or dipyridamole thallium imaging[5,14].

But significant number of patients are not candidates for the these pharmacologic coronary vasodilation, especially those with asthma, severe obstructive lung disease, high grade atrioventricular block, arterial hypotension or those on use of methylxanthine or dipyridamole. Dobutamine, a beta-one specific agonist, cause a significant increase in coronary blood flow by increase in myocardial contractility without the potential to induce brochospasm or hypotension. It had been used in conjunction with either thallium imaging or echocardiography as a means of assessing coronary artery disease[7,8,15,16]. Report of dobutamine thallium imaging demonstrated favorable diagnostic accuracy for detection of coronary artery disease and a good safety profile[7,8].

The myocardial thallium kinetics after these pharmacologic interventions may be different from that after exercise stress test, and may also be different between each others. Because the systemic and regional hemodynamic effects of these different stress may differ due to differences in the pharmacologic action. Several studies compared thallium kinetics during dipyridamole or adenosine infusion with that of exercise test[17,18].

But there is a limited knowledge about thallium kinetics during dobutamine infusion. Furthermore no group of investigators has compared all of these different during intervention in the same group of

subjects.

This study was designed to determine the differences in the thallium kinetics following standard doses of intravenous dipyridamole, adenosine and dobutamine in healthy subjects. We performed thallium myocardial imaging after intravenous infusion of dipyridamole, adenosine, and dobutamine, and exercise stress testing in the same group of 15 healthy subjects. We then compared the regimens with special regards to the hemodynamic changes and myocardial and extracardial thallium kinetics.

## METHODS

### 1. Study Subjects

The study group comprised 15 healthy male volunteers aged 23-30. These subjects were nonsmokers and took no current medications. None had a history of cardiovascular disease or other systemic significant illness. All had normal physical examination findings, electrocardiograms and plain chest radiogram. Our study protocol was approved by the Review Board of the University Hospital. Subjects gave written consent prior to study entry. Anticipated whole body and renal dosimetry for the four times of thallium test was 1.2-2.8 rem/8 mCi and 8 rem/8 mCi respectively of thallium-201.

### 2. Study Protocol

All fifteen volunteers underwent thallium-201 myocardial perfusion scintigraphy four times, first, in conjunction with the Bruce protocol exercise stress test, and subsequently with resting intravenous adenosine, dipyridamole, and dobutamine infusion in a sequence that was varied. All subjects fasted overnight prior to scintigraphy, but soft beverages without caffeine were permitted between stress and rest imaging. Mean duration of time between examinations was 15 days, with a range of 10-32 days.

### 3. Stress Thallium-201 Imaging Protocols

At the beginning of the each test, a peripheral intravenous line was established. Heart rate, blood pressure and a 12 lead electrocardiogram were monitored throughout the procedure. Two mCi (74MBq) of thallium was injected during each test. The does of thallium injected was precisely determined with a dose calibrator (Capintec CRC-12) by measuring the radioactivity in the syringe before and after administration. When administrating adenosine or dobutamine, one intravenous line with a dual port was used for protecting bolus delivery if the radiopharmaceutical was injected rapidly through the same intravenous line. The side effects that subjects experienced during procedure were recorded. In addition, subjects were asked to rank the pharmacologic test regards to tolerability.

Exercise thallium imaging: Subjects performed maximal, symptom-limited graded treadmill exercise according to the standard Bruce protocol. All subject achieved at least 85% of their maximal predicted heart rate (220 beats-age in year). At peak exercise thallium was injected and the subjects continued to exercise for 1 minute longer. Imaging began within 5 minutes of the cessation of exercise.

Adenosine thallium imaging: Adenosine (adenosine powder, Sigma, USA) was dissolved in 0.9% NaCl and prepared for intravenous human use by the pharmacy of Kyungpook National University Hospital, in a concentration of 3 mg/ml. Adenosine was intravenously administered with an infusion pump at a rate of 0.14 mg/kg body weight for 6 minutes. At the end of third minute of infusion, thallium was injected. Imaging began within 10 minutes after thallium injection.

Dipyridamole thallium imaging: Dipyridamole (Persantine, Behringer-Ingelheim, USA) was infused at a rate of 0.14 mg/kg body weight per minute for 4 minutes. Three minute later thallium was injected intravenously, and stress images were acquir-

ed 5 minutes after thallium injection. Intravenous aminophylline was kept available for the reversal of severe side effects but was not required.

Dobutamine thallium imaging: Dobutamine (Dubutrex, Lilly, USA) was infused at a rate of 5 ug/kg/min for 3 minutes followed by stepped increase to 10, 20, 30 and 40 μg/kg/min for each consecutive 3 minutes. Thallium was injected at the 1 minute following initiation of the maximal tolerable dose, and continued infusion of dobutamine for 2 minutes. Imaging began after 5 minutes of thallium injection. Esmolol was kept available for the reversal of serious side dffects but never used.

### 4. Planar Thallium Acquisition

Thallium-201 myocardial perfusion imaging was performed in the anterior, 45-degree left anterior oblique and 75-degree left anterior oblique views initially and 4 hour after thallium administration. The imagings were recorded for 8 minutes with a standard scintillation camera with a parallel hole collimator and interfaced with a computer system (Microdelta, Siemens). A 20% energy window centered on the 68-80 KeV and a 10% window centered on the 167 KeV peak were used. All images were stored on computer in a 128×128 matrix.

### 5. Quantitation of Thallium Uptake and Clearance

Thallium-201 myocardial and extracardial uptake were calculated quantitatively by use of two methods with and without background subtraction.

With the first approach, absolute thallium uptake and clearance without background subtraction was determined. A total of 17 regions of interest, 7 cardiac and 10 extracardiac, were obtained. Regions in the anterior view were anterolateral myocardium, inferior myocardium, lung, sternum, liver and splanchnic regions. In the left anterior 45-degree projection, regions included the posterolateral myocardium, septum, right ventricle, lung, liver and spleen. In the left anterior oblique 75-degree projection, inferior and anterior myocardium, lung, splanchnic region and spleen were included. A 6×6 pixel box was selected in each region. Absolute uptake of cardiac and extracardiac regions was represented as the average count numbers per pixel. For each region, thallium clearance (percent per hour, %/hr) occuring between the stress and delayed images was calculated as the rate of change in average counts per pixel. The exact times of the delayed images relative to the early images were measured on an individual patient basis. With a second method, relative uptake and clearance of thallium were calculated with background subtraction by mean of computer procedure that had been previously described[19]. An elliptical region of interest was placed around the left ventricle and the region corresponding to the left ventricle and the region corresponding to the value plane excluded. Background subtraction and determination of thallium activity were determined in 6 regions of projection (anterolateral and inferior wall in anterior view, septum and posterolateral wall in left anterior oblique 45-degree view, and anterior and inferior wall in left anterior oblique 75-degree view), placed in the left ventricular wall from the stress and delayed images. Myocardial count activities were normalized to the hottest individual pixel region in the stress view and were presented as a percent of relative thallium uptake. Thallium clearance (percent per hour, %/hr) occuring between images was calculated as the rate of change in segmental counts.

### 6. Statistical Analysis

Data were expressed as mean ± standard deviations unless stated otherwise. The means of hemoynamic data for the pharmacologic intervention were compared with each others and with those of the exercise stress test. The effects of dipyridamole, adenosine, dobutamine and exercise stress test on thallium kinetics in same subject were

compared, seperately. We analyzed our results using the SPSS-PC+ statistical software program (SPSS Inc, Chicago, II). Continuous variables were compared using the paired t-test, and dichotomous variables were compared using chi-square analysis. A p value $<0.05$ was considered statistically significant.

## RESULT

### 1. Hemodynamic Response

The mean heart rate, blood pressure and double product (heart rate × systolic blood pressure) were similar before exercise and pharmacologic interventions. Mean exercise duration of 15 subjects were 12.9+1.7 min (12.1+1.3 Mets), and all stopped exercising because of physical exhaution. Exercise increased heart rate, blood pressure and double product significantly. Adenosine and dipyridamole decreased blood pressure mildly, and increased double product. Heart rate, blood pressure and double product were increase during maximal doses of dobutamine. At peak stress, blood pressure, heart rate and double product reached significantly higher levels during dobutamine infusion compared with the levels seen during infusion of the other two drugs ($p<0.01$). Double product during exercise was higher than dobutamine ($p<0.01$), whereas the levels observed during adenosine and dipyridamole infusions did not differ significantly (Table 1).

### 2. Side Effects of Pharmacologic Stress Tests

No serious side effects occured during the tests. No specific intervention for side effect was required. Premature termination before reaching a maximal dose of the drug occurred in one subject during dobutamine infusion. Dobutamine infusion was

**Table 1. Hemodynamic Responses in 15 Healthy Subjects**

| | Exercise | Adenosine | Dipyridamole | Dobutamine |
|---|---|---|---|---|
| Heart rate (beats/min) | | | | |
| Baseline | 64 ± 7 | 63 ± 8 | 64 ± 11 | 62 ± 8 |
| Maximum | 186 ± 12 | 79 ± 19 | 82 ± 11 | 92 ± 29 |
| P value | < 0.001 | < 0.001 | < 0.001 | < 0.001 |
| Systolic BP (mmHg) | | | | |
| Baseline | 109 ± 11 | 112 ± 7 | 115 ± 10 | 110 ± 10 |
| Maximum | 162 ± 14 | 109 ± 10 | 111 ± 10 | 175 ± 27 |
| P value | < 0.001 | NS | NS | < 0.001 |
| Diastolic BP (mmHg) | | | | |
| Baseline | 67 ± 9 | 70 ± 8 | 71 ± 8 | 69 ± 8 |
| Maximum | 83 ± 8 | 65 ± 5 | 70 ± 9 | 81 ± 16 |
| P value | < 0.001 | < 0.05 | NS | < 0.01 |
| Double product (mmHg x Beats/min) | | | | |
| Baseline | 6990 ± 976 | 7064 ± 1198 | 7378 ± 1487 | 6784 ± 778 |
| Maximum | 30093 ± 2546 | 8669 ± 2501 | 9118 ± 1557 | 15441 ± 2486 |
| P value | < 0.001 | < 0.001 | < 0.001 | < 0.001 |
| Exercise capacity (duration) | 12.1 ± 1.3 Mets (12.9 ± 1.7 minutes) | | | |

Data are mean ± S.D. NS : not significant.
BP : Blood pressure, Double product = systolic blood pressure x heart rate.
* Double product : exercise > dobutamine > dipyridamole, or adenosine ($P < 0.01$ respectively).

stopped at a dose of 30 ug/kg because of complex ventricular extrasystole in this patient, but subsided without treatment within three minutes once the infusion was stopped. The rates of symptom were higher: 13 of 15(87%) subjects with adenosine, 12 of 15(80%) subjects with dipyridamole, and 11 of 15 (73%) subjects with dobutamine, respectively(p= nonsignificant). The common side effects were chest pain, flushing, headache, and choking sensation on throat for adenosine, and headache, chest pain, and flushing for dipyridamole, and palpitation, chest discomfort, headache for dobutamine, respectively. Most subject graded these symptoms as mild and transient in nature. First degree atrioventricular block appeared in one during adenosine. More subjects preferred adenosine(9/15, 60%) as the most tolerable agent than dipyridamole(4/15, 27%, $p = 0.01$) or dobutamine(2/15, 13%, $p = 0.01$). More subjects(10/15, 67%) ranked dobutamine as the most intolerable agent, than adenosine(3/15, 20%, $p = 0.01$) or dipyridamole(2/15, 13%, $p = 0.01$) (Table 2).

### 3. Absolute Myocardial and Extracardiac Thallium Uptake and Clearance

Qualitative interpretation of images showed no perfusion defects or redistribution in any of the 15 subjects during exercise stress test or pharmacologic interventions. Multivariate analysis of variance demonstrated that the absolute myocardial and extracardiac thallium uptake in the stress imaging after pharmacologic interventions for the 17 regions differed from that after exercise. Uptake of thallium were significantly greater after dipyridamole, adenosine or dobutamine than after exercise stress in most of cardiac regions except in several regions. Absolute thallium uptake were not different from that after exercise stress in inferior wall of anterior view after adenosine, in posterolateral wall after dipyridamole, and in anterolateral wall after dobutamine. Mean absolute uptake in projection with adenosine, dipyridamole, or dobutamine were greater than that with exercise test. Mean absolute myocardial uptake was greater with adenosine than that with dipyridamole, and it was greater with dobutamine than that with adenosine. But these differences were not statistically significant. Uptake were also significantly greater after pharmacologic interventions in the extracardiac regions of the sternum, lung, splanchnic region and spleen.

Thallium clearance after adenosine, dipyridamole and dobutamine infusion differed from that after exercise test for the 17 regions. Clearance were significantly slower after pharmacologic interventions than after exercise test in most myocardial regions. But myocardial clearances in anterior and

**Table 2. Side Effects of Pharmacologic Interventions in 15 Subjects**

| Adenosine | (n) | Dipyridamole | (n) | Dobutamine | (n) |
|---|---|---|---|---|---|
| Chest pain | 10 | Headache | 11 | Palpitation | 7 |
| Flushing | 8 | Chest pain | 8 | Chest discomfort | 5 |
| Headache | 5 | Flushing | 7 | Headache | 4 |
| Chocking on throat | 5 | Choking on throat | 3 | Facial numbness | 3 |
| Dizziness | 2 | Dyspnea | 1 | Chilling | 3 |
| 1° heart block | 1 | Epigastric pain | 1 | Nausea | 3 |
| Epigastric pain | 1 | | | Anxiety | 2 |
| | | | | Arrhythmia | 1 |
| Any symptom | 13 (87%) | | 12 (80%) | | 11 (73%) |

n : number, * Multiple ventricular extrasystole.

**Table 3. Absolute T1–201 Uptake of Stress Image (Average Counts/Pixel) in 15 Subjects**

| Projection | Region | EST | AD | DP | DBT |
|---|---|---|---|---|---|
| ANT | Anterolateral | 408 ± 58 | 501 ± 94** | 477 ± 103*** | 501 ± 78 |
| | Inferior | 410 ± 54 | 510 ± 96 | 504 ± 113*** | 544 ± 81** |
| | Lung | 115 ± 14 | 192 ± 21* | 191 ± 25* | 183 ± 20 |
| | Sternum | 74 ± 8 | 169 ± 21* | 176 ± 17* | 167 ± 15** |
| | Liver | 109 ± 20 | 442 ± 76* | 440 ± 79* | 504 ± 46** |
| | Splancnic | 117 ± 29 | 478 ± 76* | 467 ± 101* | 421 ± 75* |
| LAO 45° | Posterolateral | 387 ± 47 | 508 ± 89** | 493 ± 95 | 537 ± 92** |
| | Septum | 389 ± 52 | 531 ± 109* | 518 ± 108* | 558 ± 99* |
| | Right ventricle | 209 ± 22 | 365 ± 60* | 392 ± 95* | 401 ± 54* |
| | Lung | 106 ± 18 | 184 ± 28* | 187 ± 31* | 185 ± 24* |
| | Liver | 112 ± 18 | 376 ± 80* | 361 ± 78* | 347 ± 49* |
| | Spleen | 130 ± 33 | 397 ± 88* | 780 ± 84* | 347 ± 49* |
| LAO 75° | Anterior | 340 ± 42 | 497 ± 95* | 456 ± 75* | 460 ± 89* |
| | Inferior | 362 ± 39 | 524 ± 94* | 503 ± 77* | 526 ± 75* |
| | Lung | 104 ± 15 | 173 ± 26* | 171 ± 25* | 171 ± 20* |
| | Splancnic | 133 ± 31 | 449 ± 88* | 429 ± 107* | 397 ± 61* |
| | Spleen | 121 ± 12 | 338 ± 82* | 314 ± 52* | 328 ± 54* |

* : $P < 0.001$, ** : $P < 0.01$, *** : $P < 0.05$ significantly different from EST.
EST : exercise stress test, AD : Adenosine, DP : Dipyridamole, DBT : Dobutamine.
LAO : left anterior oblique.

**Table 4. Absolute Clearance of T1–201 of Various Organs in 15 Subjects**

| Projection | Region | EST | AD | DP | DBT |
|---|---|---|---|---|---|
| ANT | Anterolateral | 12.9 ± 1 | 9.8 ± 1.7* | 9.7 ± 2.2** | 11 ± 1.9 |
| | Inferior | 13.0 ± 1.3 | 9.7 ± 1.7** | 10.1 ± 2.3** | 11.6 ± 1.7** |
| | Lung | 7.9 ± 1.7 | 9.8 ± 1.2*** | 10.4 ± 1.2** | 8.7 ± 1.5 |
| | Sternum | −1 ± 3.5 | 5.0 ± 1.5* | 6.0 ± 1.3** | 5.2 ± 1.2** |
| | Liver | −3 ± 6 | 14 ± 1.8* | 14.9 ± 1.7* | 14.2 ± 2.6* |
| | Splanchnic | −1.2 ± 5.5 | 12 ± 2.6* | 12.5 ± 3.7* | 11.5 ± 1.7** |
| LAO 45° | Posterolateral | 12.4 ± 1.1 | 10.3 ± 1.5** | 10.4 ± 2.3** | 11.3 ± 1.5*** |
| | Septum | 12.0 ± 1.0 | 10.3 ± 1.9** | 10.5 ± 2.3 | 11.4 ± 1.6* |
| | Right ventricle | 9.5 ± 1.4 | 11.6 ± 1.1** | 12.8 ± 2.2* | 11.4 ± 3.5* |
| | Lung | 4.9 ± 2.2 | 7.6 ± 1.3*** | 8.1 ± 1.6** | 7.2 ± 2 1** |
| | Liver | −1 ± 4.4 | 13.2 ± 1.7* | 13.8 ± 1.5* | 13.8 ± 1.2* |
| | Spleen | 1.4 ± 4.2 | 12.1 ± 1.3* | 12.4 ± 1.6* | 10.4 ± 1.3* |
| LAO 75° | Anterior | 11.7 ± 1.2 | 11.0 ± 1.9 | 10.8 ± 1.9 | 11.3 ± 1.8 |
| | Inferior | 11.7 ± 1.2 | 10.7 ± 1.6 | 11.0 ± 1.6 | 11.5 ± 1.3 |
| | Lung | 4.8 ± 1.5 | 9.1 ± 1.5* | 8.2 ± 4.4* | 8.0 ± 1.4* |
| | Splanchnic | 0.1 ± 4.9 | 10.6 ± 2.5* | 10.8 ± 2.5* | 9.8 ± 1.5* |
| | Spleen | 1.2 ± 3.0 | 11.5 ± 2.8* | 11.4 ± 1.6* | 10.4 ± 3.0* |

* : $P < 0.001$, ** : $P < 0.01$, *** : $P < 0.05$ significantly different from EST.
EST : exercise stress test, AD : Adenosine, DP : Dipyridamole, DBT : Dobutamine.
LAO : left anterior oblique.

inferior wall of left anterior oblique 75-degree view were not different between pharmacologic stress and exercise test. Clearance were significantly faster after pharmacologic interventions in the extracardiac regions of the lung, liver, splanchnic region and spleen. But no significant differences were in clearance for myocardial and extracardiac regions between adenosine, dipyridamole and dobutamine (Table 3, 4).

### 4. Relative Myocardial Uptake and Clearance

Calculated relative thallium uptake in the stress imaging did not differed in most of myocardial regions after pharmacologic intervention compared with that after exercise test. Three were no significant difference in relative myocardial uptake between adenosine, dipyridamole and dobutamine infusion. Thallium uptake were lesser in anterolateral wall of adenosine imaging, and inferior wall of dipyridamole imaging than those of exercise imaging.

Relative clearance were different between myocardial regions with adenosine, dipyridamole, dobutamine and exercise stress test. Clearance were significantly lower after adenosine, dipyridamole or dobutamine than that after exercise stress, respectively. Clearance after dobutamine was higher than that after adenosine or dipyridamole, but differences were not statistically significant. Segmental myocardial clearance were higher after pharmacologic stress in images of anterior, or 30-degree oblique view than that of 75-degree oblique view. The overall clearance rates were significantly lower in the groups with pharmacologic intervention compared with those of exercise stress in each projection (Table 5, 6).

**Table 5. Myocardial Uptake of T1—201 after Background Subtraction**

| | Exercise | Adenosine | Dipyridamole | Dobutamine |
|---|---|---|---|---|
| Anterolateral | 256 ± 36 | 237 ± 70* | 202 ± 64 | 230 ± 65 |
| Inferior# | 235 ± 32 | 197 ± 55 | 177 ± 60* | 198 ± 63 |
| Posterolateral | 232 ± 31 | 197 ± 53 | 201 ± 58 | 227 ± 62 |
| Septal | 226 ± 36 | 229 ± 63 | 216 ± 69 | 230 ± 75 |
| Anterior | 195 ± 29 | 216 ± 54 | 197 ± 48 | 198 ± 55 |
| Inferior## | 218 ± 24 | 217 ± 54 | 213 ± 51 | 223 ± 48 |

* : $P < 0.01$, significantly different from exercise.
# : Anterior view, ## : LAO 75° view.

**Table 6. Myocardial Clearance of T1—201 after Background Subtraction**

| | Exercise | Adenosine | Dipyridamole | Dobutamine |
|---|---|---|---|---|
| Anterolateral | 15.4 ± 1 | 8.8 ± 3.9* | 6.8 ± 5.1** | 11.5 ± 3.8* |
| Inferior# | 15.8 ± 1.3 | 7.6 ± 4.6* | 6.5 ± 5.9* | 11.5 ± 3.8** |
| Posterolateral | 15.6 ± 1.2 | 8.4 ± 4.7* | 8.2 ± 5.3* | 11.9 ± 3.1* |
| Septal | 15.3 ± 1.4 | 9.1 ± 4.1* | 8.6 ± 4.6* | 11.6 ± 3.7** |
| Anterior | 14.6 ± 3.0 | 11.0 ± 2.6* | 10.9 ± 3.2** | 12.8 ± 4.3 |
| Inferior## | 15.3 ± 1.8 | 10.5 ± 2.3* | 9.9 ± 3.3* | 12.2 ± 2.9** |

* : $P < 0.001$, ** : $P < 0.01$, significantly different from exercise.
# : Anterior view ## : LAO 75° view.

## DISCUSSION

### 1. Dipyridamole, Adenosine and Dobutamine in Thallium-201 Imaging

Testing coronary flow reserve by increasing coronary blood flow using a pharmacologic method is widely accepted an alternative for those patients who cannot achieve desired stress levels with maximal exercise tests. Pharmacological stress test is effort-independent, and is more likely to deliver a maximal test of flow reserve, with a greater possibility of identifying all hemodynamically significant lesions[20]. In nuclear cardiac imaging, adenosine, dipyridamole, and dobutamine have been commonly used for this purpose.

Intravenous administration of either dipyridamole or adenosine increases levels of circulating adenosine, thus increasing coronary blood folw in normal coronary arteries. Adenosine is a potent vasodilator in most vascular beds, with exception of the kidney[21,22]. Both A1 and A2 receptors have been implicated in the coronary vasodilatory effects of adenosine. Stimulation of endothelial A2 receptors by adenosine activates guanylate cyclase, increasing cyclic GMP production and resulting in vasodilation. It has also been suggested that adenosine A1 receptor stimulation may directly induce relaxation of vascular smooth muscle. Adenosine has a rapid onset of action (reaching a maximum in 7~10 sec), and an extremely short half-life (<10 sec). Wilson et al[13] found a mean 4.4 fold increase in coronary blood flow velocity. They[13] and Rossen et al[23] demonstrated a maximal or near maximal increase in coronary blood flow at intravenous dose of up to 140 ug/kg/min of adenosine. For nuclear cardiac imaging, a 6-minute intravenous infusion of 0.14 mg/kg/min is recommanded, and thallium is administered at the end of the third minute of infusion. Dipyridamole acts as a coronary vasodilator predominantly by its effect on the small resistance vessels of the coronary bed. The primary mechanism of dipyridamole is to inhibit the cellular reuptake of adenosine and metabolism by adenosine deaminase, thus increasing the interstitial adenosine concentration[11]. The optimal protocol of dipyridamole thallium imaging has been found to be infusion of dipyridamole at a rate of 0.142 mg/kg/min for 4 minutes, and injection of thallium 3 minute after completion of infusion. Higher doses have been reported to increase the sensitivity with no loss of specificity, but side effects were more common[4]. Studies have shown that the peak effect of dipyridamole occurs approximately 2~3 minutes after infusion and it remains at this level for approximately 30~60 minutes[3,4,24]. Rossen et al[23] compared adenosine with dipyridamole and showed that the vasodilatory potency of adenosine is greater than that of dipyridamole, though increases in flow were similar between the two agents. They concluded that the rapid onset of action of adenosine compared with that of dipyridamole may allow a reduction in the duration of diagnostic studies. Dobutamine is a synthetic sympathomimetic amine, with predominant beta-one agonist activity resulting in increased myocardial contractility and left ventricular oxygen consumption. At higher doses (>20 ug/kg/min), dobutamin may have some beta-two and alpha adrenergic effects as well, with resultant increases in heart rate and systolic blood pressure[25,26]. The pharmacokinetic profile of the dobutamine is favorable in that the tissue half-life of the drug is about 2 minutes, and the mean duration of action is less than ten minutes. Infusion up to 40 ug/kg/min have been safely used[8]. The protocol commonly used, even though not well established, is infusion of dobutamine at three minute intervals in the following increments: 5 ug/kg/min, 10 ug/kg/min, then 20, 30 and 40 ug/kg/min. At one minute following the initiation of the maximal dose, thallium is injected intravenously. The dobutamine infusion is then continued for an additional two minutes if tolerated and then discontinued.

### 2. Hemodynamic Changes, Heart Rate and Double Product

Hemodynamic changes were similar to those reported after use of pharmacologic stress agents. Dobutamine increases heart rate, blood pressure, and dobule product. Adenosine and dipyridamole also increase heart rate and double product, but not to the same extent as dobutamine, and decrease blood pressure mildly. The double product was more than 50% higher with compared with adenosine and dipyridamole, suggesting that myocardial oxygen demand was higher with dobutamine. Martin et al[27] demonstrated hemodynamic data similar to ours, with the comparison of adenosine, dipyridamole, and dobutamine echocardiography in 40 patients. In our normal subjects, the double product was lower during dobutamine infusion since though the systolic blood pressure increased to a extent, the increase in heart rate was lesser than exercise. Mannering et al[28] compared the effect of dobutamine infusion , at a maximal dose of 20 ug/kg/min, with that of exercise stress test in patients three weeks after myocardial infarction. They showed that the heart rate and double product increases more during dobutamine infusion, while maximal acceleration in the ascending aorta increases more during dobutamine infusion than during exercise. They suggested the ischemia produced during dobutamine infusion therefore seems to be caused predominantly by an increase in the inotropic state rather than through an increase in heart rate, as it is during exercise.

### 3. Side Effects

Side effects were frequent during the pharmacologic stress but were well tolorated and short-lived. No specific antidote was used to reverse serious side effects throughout the procedures. Maximal dose of drug could not be acquired only one subject during dobutamine infusion because of multiple extrasystole. Dobutamine has been found to increase the risk of ventricular tachyarrythmias, especially at a higher doses. Ventricular tachyarrythmia occurred in 31% of patients in a study of dobutamine echocardiography[30]. However, of currently used catechol compounds, it is the least likely to do so[25,26]. The rates of side effects were not significantly different: 13 of 15 subjects had at least one symptom during adenosine infusion, whereas 12 of 15 during dipyridamole infusion and 11 of 15 during dobutamine infusion. In patients with suspected coronary artery disease the reported rate of side effects with adenosine had ranged from 83% to 94%[5,6,14], and the range with dipyridamole has been reported from 46% to 62%[3,4,12]. The rate of side effects with dobutamine was 80% in a recent study[30]. More subjects prefer adenosine(60%) than dipyridamole(27%) or dobutamine(13%). Moreover, 10 of 15(67%) of subjects ranked dobutamine the most intolerable agent among three drugs. Most of these subjects complained that they experienced unpleasant feelings of profound palpitation, nervousness, and thrill sensation during dobutamine infusion. Martin et al[27] compared these three drugs in regards to tolerance in patients, and reported that more patients prefered dobutamine than adenosine or dipyridamole. We found, at least in normal subjects, adenosine is the most tolerable agent among three drugs, although study sample was small for adequate statistical analysis.

### 4. Myocardial Thallium Uptake and Clearance

Myocardial uptake of thallium-201 in normal subjects was greater after pharmacologic stress compared with that after exercise stress. Mean absolute myocardial uptake in all projections was 1.3 times greater after adenosine than exercise, and 1.2 times greater with dipyridamole. Furthermore, mean absolute myocardial uptake with dobutamine was 1.4 times greater than that after exercise. Myocardial thallium uptake tended to be greater

with dobutamine, or adenosine than that with dipyridamole, but differences were not statistically significant. These results are comparable to reported uptake data of adenosine and dipyridamole[17,18]. But, within our knowledge, no comparison of myocardial thallium uptake has been performed with dobutamine and that with exercise. Our data showed myocardial uptake of thallium during dobutamine infusion, at higher doses, is comparable to those with adenosine and dipyridamole. These differences in myocardial thallium uptake may reflect several aspects of the differing hemodynamic effects of pharmacologic stress and exercise. Myocardial uptake of thallium is related to coronary blood flow as a fraction of cardiac output. Merlin et al elucidated that under different flow and metabolic conditions, the early fractional uptake of thallium by the left ventricle is a reasonably good appoximation of myocardial blood flow[31]. The ratio of coronary blood flow to cardiac output are greater during adenosine or dipyridamole infusion, compared with that during exercising. This would favor greater myocardial thallium uptake after adenosine and dipyridamole. The increase in coronary blood flow are 3 times baseline value with adenosine, and 2.4 to 5 times with dipyridamole, which are greater the increase with exercise of 1.7 to 2.5 times baseline[13,17,32~34]. Adenosine causes a smaller increase in cardiac output, reported to be 2 to 3 times baseline value, compared with three to fivefold increase at exercise[13,20,35]. The increase in cardiac output with dipyridamole is reported to be 1.3 times baseline value[32]. Because dipyridamole and adenosine act through similar mechanisms, our results suggest that the doses commonly used were not accurately equivalent in pharmacologic action. Dobutamine produces hemodynamic changes similar to exercise. In patients with and without coronary artery disease, dobutamine shows dose-dependent increase in coronary blood flow, cardiac output and left ventriscular contractility and to a lesser extent, heart rate and mean arterial pressure[25,36,37]. Meyer et al[38] and Stephen et al[36] reported that, during the infusion of dobutamine at a rate of 8 ug/kg per minute, the patients with normal coronary arteriograms had a 137 percent in coronary perfusion. Based upon our data, the ratio of coronary blood flow to cardiac output may be greater with dobutamine at larger doses up to 40 ug/kg per minute, than that has reported in patients with infusion at lower dose. The thallium uptake does not solely depend on blood flow. The myocardial thallium uptake is proportional to the blood flow if flow changes are secondary to metabolic demand, but the increase in coronary flow in excess of myocardial demands, as in pharmacologic vasodilation with adenosine or dipyridamole, results in a progressive decrease in thallium extraction[40,41]. Which et al[41] found a logarithmic decrease in thallium uptake where coronary blood flow was increased in excess of oxygen demands. Dobutamine is a cardioselective inotropic agent that increases myocardial contractility and oxygen demand significantly. Thus myocardial extraction rate of thallium may be preserved higher after dobutamine compared with that after pharmacologic vasodilation. This may partially explains that myocardial uptake of thallium is comparable after dobutamine to those after adenosine or dipyridamole. Increased absolute myocardial uptake with pharmacologic stress also may be partially due to increased background uptake seen in our reaults, that will be discussed later.

Myocardial thallium clearance were slower after three drugs than that after exercise stress in most of myocardial regions. But no significant differences were in myocardial clearance in regions of LAO 75° view, the most delayed view in stress imaging. Early myocardial clearance seen in exercise thallium imaging may attribute this result in this view taken more than 20 minutes after completion of exercise. There were no significant differences in myocardial clearance of thallium among adenosine, dipyr-

idamole and dobutamine, even though clearance with dobutamine tended to be slightly faster. O'Byrne et al and Beller et al demonstrated that the value of thallium clearance is slower with dipyridamole than that with exercise[42,43,44]. Siffring et al[18] showed that adenosine tended to cause slower clearance of thallium compared than exercise. This has been reported due to lower myocardial-blood gradients of thallium because the initial myocardial uptake were higher during pharmacologic stress. Experimental data suggested that the myocardial clearance of thallium is related to the myocardial blood-pool gradient of thallium activity such that delivery of a greater amount of myocardial thallium initially will result in its being cleared faster[43,45]. The continued elevation and slower clearance of blood thallium also has been elucidated in a study[17]. In exercise thallium imaging, the peak execise heart rate has been suggested to bear a positive relationship with thallium myocardial clearance[46,47].

### 5. Extracardiac Thallium Uptake and Clearance

Extracardiac uptake of thallium were greater with pharmacologic stress than exercise stress in liver, spleen and splanchnic regions. There were no significant differences in extracardiac regions between adenosine, dipyridamole and dobutamine. The differences in regional thallium uptake after pharmacologic stress and exercise are most likely related to regional blood flow differences. With exercise in human, the increase in cardiac output is proportioned mainly to the exercising muscles. Studies have shown a reduction in splanchnic and renal blood flow that is roughly proportional to the level of exercise[48]. In contrast, regional blood flow after pharmacologic vasodilation with adenosine or dipyridamole are much similar to that of the rest state. Adenosine and dipyridamole decrease not only coronary but also systemic vascular resistance. Brown et al[32] measured systemic vascular resistance before and after dipyridamole infusion and showed a decrease from 15±5 mmHg/liter/min to 10.9±4.0 mmHg/liter/min. This results in increased thallium uptake in the regions of the splanchnic circulation, liver and spleen. Dobutamine cause a redistribution of cardiac output in favor of the coronary and limb beds over the mesenteric and renal vascular bed[39,49]. Dobutamine is a direct acting agent with selective for beta-1 receptor, and its indirect actions are slight. In animals, dobutamine, administered at a rate of 2.5~15 ug/kg/min, increases cardiac contractility and cardiac output, without changes in total peripheral resistance[26]. But, at higher doses (>10 ug/kg/min) commonly using in thallium imaging, tachycardia and changes in peripheral vascular resistance occurs because of activation of beta-2 and alpha adrenergic receptors[25,26]. This may cause a higher uptake of thallium in splanchnic regions liver and spleen after dobutamine infusion. Increased thallium uptake in the liver yields myocardial images with high infradiaphragmatic background activity[50,51]. Lung uptake of thallium were also greater after pharmacologic stress than that after exercise stress. This may be related to the longer pulmonary transit time associated with the lower heart rates during pharmacologic stress seen in our data, which results in less time for thallium extraction. Lung uptake of thallium has been reported to be greater after dipyridamole than that after exercise[52], but Siffring et al reported no significant differences in lung uptake between adenosine and exercise. Ruddy et al[17] found the blood levels of thallium was higher after dipyridamole infusion than that after exercise test, and suggested that the greater thallium blood levels after dipyridamole infusion also resulted in higher tissue levels of thallium in all regions.

In our study, extracardiac thallium clearance from the liver, splanchnic region, and spleen were greater after pharmacologic stress than that after exercise stress. Furthermore, clearance from the lung and

sternal regions were also higher after pharmacologic stress test, even though it was slower than that of myocardium. This may also be related to higher initial uptake of thallium in these regions. Ruddy et al[17] reported that the thallium clearance from lung is not significantly different with dipyridamole from that with exercise test, a result related to the lower tissue-blood gradients after dipyridamole infusion compared with that after exercise stress. Bull et al[52] calculated that skeletal muscle accumulates about two-thirds of the thallium injected at a peak exercise. In contrast, the extracardiac uptake of thallium occurs primarily by the liver, spleen and splanchnic circulation. The prolonged persistence of high levels of blood thallium after dipyridamole, attributed to the rapid early rapid clearance from the splanchnic and liver reservoir, has been proposed[17,52]. We did not measure blood levels of thallium during these pharmacologic intervention, and further clarification is needed for this concept in the same group of subjects. Myocardial uptake and clearance after background subtraction.

Calculated myocardial uptake of thallium were not different after background subtraction between pharmacologic stress tests and exercise test. Myocardial clearance was higher after background subtraction after exercise test than that after pharmacologic tests. But, there were no significant differences in relative myocardial uptake and clearance between adenosine, dipyridamole, and dobutamine infusion, respectively. Background activity comprised lung activity for the anterolatral, septal, posterolateral and anterior regions and splanchnic activity for the inferior and apical regions. Subtraction of greater background activity from myocardial segment after pharmacologic tests may be related to these differences in relative myocardial uptake. But, if excessive background subtraction was having a major effect, the myocardial segment adjacent to high background area, inferior or apical segments after pharmacologic stress, would tend to produce slower clearance. Segmental myocardial clearance were similar to that without background subtraction in each group suggesting this effect trivial. A study[17] showed that background subtraction has no significant segmental effect on clearance in either dipyridamole infusion or exercise stress. Interestingly, we found that there is a progressive increase in segmental myocardial clearance in sequential imaging after pharmacologic stress. In contrast, no differences were in sequential imaging after exercise stress test. We think this may be related to higher initial uptake and faster clearance of thallium from the splanchnic and liver reservoir, occurs during pharmacologic stress testing. A report suggested that peaking of myocardial thallium activity may be delayed for 20 minutes after dipyridamole[32]. This results in excessive subtraction of background from submaximal myocardial activity in early stress images, whereas smaller extraction from maximal activity in later images. In contrast, during exercise testing, thallium localizes in the exercising muscle, and it retains longer than it is in splanchnic beds during dipyridamole infusion.

## CONCLUSION

The results of the present study support that pharmacologic stress test with intravenous infusion of adenosine, dipyridamole or dobutamine is safe and favorable in thallium-201 myocardial perfusion imaging. A previous study[54] showed that dobutamine may be a superior agent for imaging modalities that rely on functional assessment, such as echocardiography. In contrast, pharmacologic vasodilator such as adenosine or dipyridamole may be the pharmacologic agent of choice, hence it induces greater blood flow heterogeneity. In our data at a standard dose, at least thallium kinetics after intravenous infusion of dobutamine is comparable to those after adenosine and dipyridamole in same normal subjects, suggesting that the

dobutamine thallium imaging is feasible. Furthermore myocardial thallium kinetics after pharmacologic stress test were different from that after execise stress test, and among those with adenosine, dipyridamole and dobutamine. These differences in thallium kinetics during different interventions suggest that the need for specific normal files for each type of stress are required when quantitative analysis of myocardial perfusion imaging is used.

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