Enhanced detection of ischaemic but viable myocardium by pharmacological stress agent with re-injection protocol thallium-201 SPECT study: A preliminary experience report

Hoque R, Britton KE

Abstract
The identification of ischaemic but viable myocardium by thallium exercise scintigraphy is widely practiced. Thallium study can predict the location of the myocardium affected by impaired perfusion and can assess the severity, extend and reversibility of the lesion. The conventional exercise-stress, redistribution and rest thallium scintigraphy is often imprecise, since many of the perfusion defects that develop the ischaemic myocardium doing exercise do not "fill-in" on subsequent redistribution images. On the other hand conventional exercise protocol provided by exercise on a bicycle stress table or treadmill does not allow a significant proportion of the patient. Considering these two major problems, we studied 7 patients with Coronary Artery Disease (two of them have only atypical chest pain with normal exercise ECG, 5 patient have CAD with history of myocardial infarction and angioplasty, stent in situ) following stress thallium study with pharmacological stress agent adenosine and re-injection of thallium 3 hours after the stress. Significant reversible myocardial ischaemia was observed in different segments in five patents, the other two patients have irreversible fixed defects. The datas indicates that the thallium study with pharmacological stress agent adenosine improves the detection of ischaemic myocardium and that myocardial region with improved thallium uptake on re-injection imaging represents viable but jeopardized myocardium.

Introduction
The use of physical effort in the diagnosis of coronary artery disease was originally described by Mark1 who recorded electrocardiographic changes in patients during episodes of pain associated with chronic stable angina. Since that time, treadmill or bicycle exercise has been used widely in conjunction with ECG, echocardiography, and scintigraphic imaging to diagnose myocardial ischemia, cardiac wall motion abnormalities, or coronary perfusion defects. Yet diagnostic accuracy of these procedures can be limited by problems inherent in echocardiography or scintigraphic imaging during or immediately following exercise2. These constraints, together with the need for alternatives to exercise in patients with peripheral vascular, respiratory, orthopedic disease3 have led to the development of pharmacological stress tests. This strategy uses agents intended to mimic certain aspects of the cardiac response to exercise, i.e., tachycardia, coronary dilation, and inotropic activation, which provoke ischemia and elicit cardiac functional changes in patients with coronary artery disease4. Exercise Thallium-201 myocardial perfusion imaging provides diagnostic information regarding the coronary artery disease, enables determination of the hemodynamic significance of known coronary lesions with respect to regional myocardial ischemia, gives an estimate of the amount of viable myocardium in patients with prior myocardial infarction, and allows for risk stratification of patients with regard to future cardiac events. However, exercise imaging is usually not practical in patients with orthopedic debilities, patients who are elderly and deconditioned, and patients with peripheral vascular disease and claudication. Pharmacological stress agents are now provides an excellent alternative to exercise. These agents are either vasodilators (dipyridamole or adenosine) or

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catecholamine (dobutamine or arbutamine). The purpose of this report is to enumerate the initial experience with pharmacological stress agent with reinjection thallium-201 myocardial perfusion imaging protocol.

Materials And Method

Patients: Seven patients over the age of legal consent, with symptoms or signs of coronary artery disease necessitating coronary angiograph or with angiographic evidence of coronary artery disease were enrolled in this study.

Screening included history and physical examination, laboratory studies and electrocardiography. Patients were excluded if they had rest ECG abnormalities, unstable angina within 6 weeks. Myocardial infarction within 30 days, a pacemaker, a history of significant arrhythmia, heart failure, cardiomyopathy and states of secondary ventricular hypertrophy, uncontrolled hypertension, aortic aneurysm or dissection, hypokalemia or other significant disease. Prohibited medications included tri-cyclic antidepressant agents, class I antiarrhythmic agents and drugs interfering with catecholamine metabolism within 1 week; and amiodarone or any investigational drug within 30 days.

Pharmacological stress agents and perfusion imaging: Adenosine is administered intravenously at a dose of 0.14 mg/kg per minute for 6 minutes. Thallium is injected at the end of the third minute. The patient’s heart rate, blood pressure, and electrocardiogram are monitored closely. Imaging is begun within 10 minutes, with delayed/redistribution imaging at 3 to 4 hours, and additional delayed or reinjection imaging was obtained. Thallium images were then obtained with a wide-field of view rotating gamma camera with SPECT facility equipped with a high-sensitivity, low-energy, medium-resolution, parallel-hole collimator centered on the 68-keV photo peak with a 20 percent window. The camera was rotated in a 180-degree arc in an elliptical orbit about the patient’s thorax from a right-anterior oblique angle of 40 degrees to a left-posterior oblique angle of 40 degrees at 6-degree increments for 30 seconds each. Redistribution images were obtained three to four hours after the pharmacological stress testing while the patients were resting. Immediately thereafter, all patients received a second injection of 1 mCi of Thallium-201, and Single Photon Emission Computed Tomography (SPECT) was performed within 10 to 15 minutes (reinjection imaging). From the raw scintigraphic data, sagittal short-axis (SAA), vertical long-axis tomo-grams (VLA) and horizontal long axis (HLA) (Fig. I) were reconstructed as previously described, 12 and four consecutive representative slices of each view were selected for interpretation. The reconstructed stress, redistribution, and reinjection images were then analyzed both qualitatively and quantitatively. Electrocardiographic and hemodynamic variables:

In this study, pharmaceutical stress agents induced exercise-like symptom-limited tests were continued to horizontal or down sloping ST segment depression or elevation unless the maximal heart rate or intolerable angina, fatigue or other adverse events occurred. The maximal heart rate for adenosine was limited by the automated device to [(220-age) X 0.85 beats/min].

The ECG, blood pressure and heart rate were continuously monitored. After stress, heart rate and blood pressure were recorded at longer intervals for 30 min or until heart rate returned to within 20 beats/min of baseline, whichever was longer.

Results

The pharmacological stress events illustrated in Table -I including change of pulse, blood pressure, and symptoms with ECG changes. Image interpretations described in Table-II, Fig. I and Fig. of cases 1 to 7 with 6 slices of three sections of heart with stress and reinjection events with individual segmental analysis.
**Table I: Baseline, stress, symptoms and ECG changes after Adenosine stress**

<table>
<thead>
<tr>
<th>Case</th>
<th>Pulse/min Baseline</th>
<th>Blood Pressure Baseline (mmHg)</th>
<th>Stress</th>
<th>ECG Changes</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>83</td>
<td>99</td>
<td>130/80</td>
<td>130/90</td>
<td>Significant ST depression and chest pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>120/70</td>
<td></td>
<td>Left bundle branch block</td>
</tr>
<tr>
<td>2.</td>
<td>92</td>
<td>125</td>
<td>110/60</td>
<td>120/70</td>
<td>Burning sensation in the chest</td>
</tr>
<tr>
<td>3.</td>
<td>68</td>
<td>92</td>
<td>140/80</td>
<td>150/70</td>
<td>No change</td>
</tr>
<tr>
<td>4.</td>
<td>64</td>
<td>84</td>
<td>135/80</td>
<td>140/90</td>
<td>No change</td>
</tr>
<tr>
<td>5.</td>
<td>96</td>
<td>110</td>
<td>165/80</td>
<td>170/85</td>
<td>T-wave inversion, ST deflection in V5-V6-T elevation V2-V3</td>
</tr>
<tr>
<td>6.</td>
<td>64</td>
<td>96</td>
<td>115/80</td>
<td>130/85</td>
<td>ST change</td>
</tr>
<tr>
<td>7.</td>
<td>74</td>
<td>92</td>
<td>105/80</td>
<td>125/85</td>
<td>Bundle branch block</td>
</tr>
</tbody>
</table>

**Table II: Image description and interpretation.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Thallium Image</th>
<th>Re-injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1. Left ventricular cavity enlarged 2. Reduced perfusion to antero-apical segment, apex to the inferior wall and septal wall 3. Perfusion to the lateral interior wall is reduced too.</td>
<td>1. Perfusion of the septum and apex is improved. 2. No improvement of perfusion of the antero-septal and inferior wall.</td>
</tr>
<tr>
<td>2.</td>
<td>1. Left ventricular cavity enlarged, reduce perfusion in the septal, antero-septal segment, apex and the inferior wall 2. Normal perfusion in the lateral wall</td>
<td>There is improvement of the Inferior Wall and apex.</td>
</tr>
<tr>
<td>3.</td>
<td>1. Left ventricular cavity is in normal size 2. There is reduced perfusion in the lateral wall 3. Elsewhere the perfusion is well.</td>
<td>Good perfusion to the myocardium</td>
</tr>
<tr>
<td>4.</td>
<td>1. Size of the left ventricle cavity is slightly enlarged 2. Reduced perfusion to the anterior wall.</td>
<td>1. Good perfusion to the anter and lateral wall of the left ventricle. 2. Ventricular cavity is normal in size.</td>
</tr>
<tr>
<td>5.</td>
<td>1. Left ventricular cavity is enlarged 2. Marked reduced perfusion to anterior, antero-septal and apical segment.</td>
<td>1. Little reduction in cavity size 2. Improvement in the perfusion of anterior wall but no improvement in antero-septal, apical, infero-apical segment.</td>
</tr>
<tr>
<td>6.</td>
<td>1. Left ventricular cavity is enlarged 2. Reduce perfusion in the lateral wall, inferior wall and apex.</td>
<td>1. Improved perfusion to lateral wall. 2. Cavity size is smaller. 3. No improvement in the perfusion in the apex and inferior wall.</td>
</tr>
<tr>
<td>7.</td>
<td>1. Left ventricular cavity size is enlarged 2. Reduced perfusion in the septal, antero-septal segment, apex, and inferior wall. There is normal perfusion in lateral wall and the apex.</td>
<td>There is improved perfusion in the Septum, partial improvement with Inferior wall.</td>
</tr>
</tbody>
</table>

**Figure 1: SPECT reconstruction slices of the heart**
Case 1: Significant reversible perfusion defect in the distal septum & the septum related apex. the antero-septal segment & the inferior wall shows a persistent defect to infarction

Case 2: Significant reversible myocardial ischaemia in antero-septal, infero-apical segments and reduction of muscle mass in the infero segment

Case 3: Normal myocardium, low probability of acute cardiac event

Case 4: Significant reversible myocardial ischaemia

Case 5: Significant reversible myocardial ischaemia at the anterior wall non reversible ischaemia of the apex and infero-apical wall

Case 6: Significant reversible myocardial ischaemia at the lateral wall with fixed inferior and apex defect
Case 7: Significant reversible myocardial ischaemia in septum, inferior wall and apex

Discussion
Thallium-201 scintigraphy has played an important part in distinguishing ischemic from infarcted myocardium in patients with coronary artery disease (CAD). Since the uptake of thallium by the myocardial cell is an active process and depends on regional blood flow, it can be used as an index of both regional perfusion and myocardial viability.

The initial uptake, or extraction of thallium in cardiac myocyte is directly proportional to regional blood flow. Thallium-201 is retained in the myocyte so long as sarcolemmal integrity and metabolic function remain intact. Over the ensuing hours, a process of exchange of thallium between the viable cells and the intravascular space goes on. Initially, hypoperfused areas have slower clearance of thallium compared to initially normal perfused areas. This results in the phenomenon of redistribution. Redistribution is defined as improvement or normalization of ischemic thallium perfusion defects with time. The presence of redistribution is a marker for myocardial ischemia and viability. On stress-redistribution imaging, fixed thallium defects were formerly equated with myocardial scarring. However many of these are "irreversible" defects did show improvement after revascularization. Thus, in patients with LV dysfunction, stress-redistribution thallium scintigraphy frequently underestimates the presence of viable myocardium and the potential for recovery.

Myocardial scintigraphy associated with pharmacological stress has been widely used for the diagnosis of CAD in patients with chest pain unable to perform adequate dynamic exercise. Among the different vasodilator pharmacological agents, adenosine has been recently used because of its short half-life (<2 min) so that patients do not experience prolonged ischemia after infusion, such as with dipyramole, and because of its more rapid action so that echocardiographic imaging may be performed early after each dose increment. Previous studies demonstrated good diagnostic accuracy of adenosine test associated with myocardial perfusion imaging in the detection of CAD. Good agreement between adenosine and dynamic exercise myocardial perfusion scintigraphy with 201-TL and 99mTc labeled agents also have been reported. Atrioventricular conduction block is particularly common with adenosine, but its duration is so brief that it is rarely necessary to give aminophylline. For patients with asthma who cannot exercise, dobutamine has been used as a stress agent for myocardial perfusion imaging, the mechanism of action of dobutamine is stimulation of beta-adrenergic receptors.

The re-injection of a small dose of thallium immediately after redistribution imaging increases the intravascular concentration of thallium to allow more exchange between the myocyte and the intravascular space and provide uptake into regions with more severely reduced blood flow.

In one study, the reinjection of thallium significantly improved the ability to detect ischemic but viable myocardium in 49 percent of the regions that were interpreted as having irreversible, fixed abnormalities on redistribution imaging. The reinjection of thallium also enhanced the uptake of the isotope in 56 percent of the regions identified as having partially reversible defects by redistribution imaging. Thus, reinjection imaging identified as viable 101 of the 172 regions that conventional stress-redistribution imaging had identified as having persistent
perfusion defects, greatly overestimating the extent and severity of myocardial fibrosis.\textsuperscript{17}

Because of very small population of this report, which preclude any firm conclusion, but there was very good agreement with the others. In our series, thallium uptake with the viable myocardium was improved after reinjection and patients tolerated well with normal exercise ECG, 5 patient have CAD with history of myocardial infarction and angioplasty, stent in situ. In recent years, studies have shown that 3-to 6-hrs redistribution myocardial perfusion imaging failed to detect reversibility of stress defects in patients who did have viable myocardium, indicated by improved regional function after revascularization 16-18 These investigators also found improved detection of viable myocardium by observing amelioration of the severity of 201-TL-imaged defects between stress images and 4- hrs redistribution images, and between images acquired 10 min after reinjection of 201-TL and the redistribution images.\textsuperscript{16-18}

The major advantage of the stress-redistribution-reinjection protocol is that it answer the clinical question of myocardial ischemia and viability in question with reversibility whether to be benefited after revascularization. The rest-redistribution technique pertains to the presence or absence of myocardial viability only. There also may be circumstances when the rest-redistribution study shows insignificant myocardial viability while the stress-redistribution-reinjection protocol brings it out.

References