

# The Clinical Utility of Thallium-201 Myocardial Perfusion Scintigraphy - A Review

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## INTRODUCTION:

With the recent introduction of Thallium-201 Myocardial Perfusion Scintigraphy (Tl-201 MPS) in a few centres in Pakistan, an additional non-invasive technique has become available for the assessment of certain parameters in patients with cardiac disorders.

To promote appropriate and optimal utilization of this technique it is desirable to have some knowledge of the biological behaviour of Thallium-201, so as to understand the potential information that can be obtained from this technique, as well as its limitations. A short description of the biokinetics of Thallium-201 and a brief review of the various clinical application of Tl-201 MPS reported in recent literature is presented.

## BIOKINETICS OF THALLIUM-201

Thallium (Tl) is a metallic element of group III A of the periodic table with properties similar to that of potassium. In terms of organ distribution too it is biologically similar to potassium<sup>(1)</sup>. Thallium-201 is the radioactive nuclide of Thallium and its radiation characteristics allow fairly successful imaging with modern day gamma scintillation camera systems in use in most Nuclear Medicine departments. After intravenous injection Tl-201<sup>+</sup> is cleared rapidly from the blood, and 5 minutes after injection, only about 5% remains in the blood. The immediate myocardial uptake is determined by the regional myocardial blood flow and the extraction of the tracer by the myocardial cells. At the cellular level Tl-201<sup>+</sup> acting as a K<sup>+</sup> analogue activates the sodium-potassium-ATPase system in the cell, resulting in cellular uptake of Tl-201<sup>+</sup> via the Na<sup>+</sup> = K<sup>+</sup> Pump.

As the extraction fraction of Tl-201<sup>+</sup> by the myocardium is approximately 88%<sup>(2)</sup>, the initial regional concentration may be considered equivalent to regional myocardial blood flow. Thus ten minutes after injection about 2-4% of the injected dose is in the heart, and in the normal individual Tl-201<sup>+</sup> is seen to be relatively homogeneously distributed throughout the myocardium of the left ventricle<sup>(3)</sup>. The right ventricle, because of its smaller myocardial mass, takes up relatively less amounts of Tl-201<sup>+</sup> and is poorly visualized on imaging. The concentration within cardiac muscle is relatively greater than adjacent organs, particularly after exercise, so that target to non-target ratio of activity allows for diagnostic imaging.

Tl-201<sup>+</sup> does not remain fixed in the myocardial cells. Following intravenous injection half of the myocardial Tl-201<sup>+</sup> will be exchanged every 75 minutes, i.e. the intrinsic half-life of Tl-201<sup>+</sup> washout from myocardium is 75 minutes. However, the net half-life of Tl-201<sup>+</sup> washout from myocardium is 7 hours. The explanation of the slower net washout rate is that after intravenous injection, as Tl-201<sup>+</sup> leaves the myocardium it is being continuously replaced by new Tl-201<sup>+</sup> from the systemic pool. This dynamic exchange allows local redistribution over time. Thus delayed accumulation of Tl-201<sup>+</sup> is seen in underperfused regions after transient coronary occlusion and also during sustained diminution of regional blood flow<sup>(4)</sup>, while a more rapid washout of Tl-201<sup>+</sup> occurs from normal segments. Redistribution of Tl-201<sup>+</sup> with time in areas of viable but hypo-perfused myocardium results in disappearance or lessening of the initial defects over the course of a few hours. However, areas of irreversibly damaged myocardium will appear as persistent regions of diminished Tl-201<sup>+</sup> concentration<sup>(5)</sup>

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## THALLIUM-201 EXERCISE MYOCARDIAL PERFUSION SCINTIGRAPHY

Because of the ability to define regions of diminished initial myocardial blood flow, and the difference in the redistribution patterns of ischaemic and infarcted zones, the major clinical utilization of Tl-201 MPS is logically in conjunction with an exercise stress test in patients with suspected or known coronary artery disease (CAD). Following intravenous injection of Tl-201<sup>+</sup> at peak exercise, the immediate post-stress images will demonstrate perfusion deficit produced both by the transient ischaemia caused by differential myocardial blood flow through stenotic coronary arteries during exercise, and by nonviable myocardium with compromised tracer extraction. Delayed images (2-4 hours post-injection) following a period of redistribution will show filling-in of defects in ischaemic areas, but persistence of the defects in regions of myocardial scarring.

### CLINICAL UTILITY:

#### TL-201 MPS IN ISCHAEMIC HEART DISEASE

The standard electrocardiographic stress test is the non-invasive technique most frequently used to diagnose CAD. However controversy over its diagnostic importance exists because false negative exercise tests are common in groups of patients with high prevalence of CAD, and false positive tests are common in groups of patients with low prevalence of such disease<sup>(6-8)</sup>.

A number of clinical studies have demonstrated the sensitivity and specificity of Tl-201 MPS to be superior to those of exercise stress ECG. Verani et al have reported the sensitivity and specificity of stress ECG, in their series, to be 65% and 62% resp., and of Tl-201 MPS to be 79% and 97%<sup>(9)</sup>. Botvinick et al gave the corresponding figures for stress ECG as 67% and 63%, and for MPS 85% and 89%<sup>(10)</sup>.

Despite the relatively low sensitivity and specificity of stress ECG, in many cases the clinical information together with the results of exercise ECG are sufficient to resolve the diagnostic problem, and management decisions can be made without the necessity of resorting to additional studies.

However in certain categories of patients ancillary tests will be required for additional information before a decision can be made. These include:

1. Patients who have a non-diagnostic or sub-optimal stress test. McCarthy et al showed that patients who failed to achieve 85% or more of the predicted heart rate, and did not develop ST depression, had a high incidence of Thallium defects on MPS despite the low work load achieved<sup>(11)</sup>.
2. Those patients with equivocal results on exercise ECG, e.g. left bundle branch block, left ventricular hypertrophy, drug effect (e.g. of digitalis) hyperventilation or other conditions. It has been shown that stress Tl-201 MPS in such patients was more accurate than stress ECG 89% versus 53%<sup>(10)</sup>.
3. Those patients with suspected false positive exercise ECG. Caralis et al studied asymptomatic patients with a normal resting ECG and a positive exercise ECG. In such patients a positive Thallium scan identified those patients with a high probability of significant CAD, whereas a normal Thallium scan even in the presence of positive ST response, placed the patient in low probability class<sup>(12)</sup>.
4. Patients with symptoms of typical or atypical angina in whom exercise ECG is normal. Thallium exercise scan can increase or decrease the likelihood of CAD in such patients<sup>(12)</sup>.

#### TL-201 MPS IN MYOCARDIAL INFARCTION

In acute myocardial infarction the detection sensitivity of Tl-201 MPS is highest (96%) within 6 to 12 hours of onset of symptoms and is greater than that of the standard ECG<sup>(13)</sup>.

Early Tl-201 MPS has proved valuable in separating high risk and low risk subgroups of haemodynamically stable patients admitted with acute myocardial infarction. It proved to be a better prognostic index than a number of clinical variables believed to be of prognostic importance, e.g. history of prior myocardial infarction, anterior location of acute infarction, high peak level of serum CK and moderate left ventricular failure. It was found to be more predictive than any

other variable and by itself was a better predictor than the best combination of clinical variables. Thus it can aid in the more aggressive and selective medical management of patients with acute myocardial infarction<sup>(14)</sup>.

This technique has also been used to evaluate patients entering coronary care units with suspected acute myocardial infarction when the initial ECG and serum enzyme measurements are non-diagnostic. It is possible to distinguish between patients with chest pain of non-cardiac origin, patients with unstable angina without subsequent infarction and patients with stable angina with subsequent infarction. This approach can result in considerable savings of high-cost intensive care beds and a more rapid application of appropriate diagnostic and therapeutic interventions to those with infarction<sup>(13)</sup>.

It has also been used to assess the effect of various therapeutic interventions during the early stages of infarction. De coster et al have studied the effects of intracoronary streptokinase therapy and found TI-201 MPS to be an accurate method for assessing reperfusion in acute myocardial infarction after successful thrombolysis<sup>(15)</sup>.

#### TI-201 MPS IN CORONARY ARTERY BY-PASS GRAFT (CABG) PATIENTS

TI-201 MPS has been used in the pre-and post-operative investigation of patients who have received bypass grafts.

In the pre-operative stage, in the presence of known CAD, both rest and exercise TI-201 studies have been used to assess viable myocardial tissue distal to a severely stenotic lesion, to evaluate the functional significance of a border line lesion, and to determine the adequacy of collateral blood supply.

In the post-operative period the success or failure of CABG is largely determined by graft patency. However, neither the symptomatic response nor the ECG response to exercise testing predicts graft patency. Thus symptomatic relief may be due not only to relief of myocardial ischaemia but also placebo effect, destruction of sensory nerves, or peri-operative infarction with resultant loss of previously ischaemic myocardium<sup>(13)</sup>.

Greenburg et al reported the relatively low sensitivity of the stress ECG alone in predicting graft occlusion<sup>(16)</sup>. Kolibash et al found that a major problem in CABG patients was the high number of indeterminate exercise ECG tests due to resting ECG changes and inability to reach an adequate heart rate<sup>(17)</sup>.

TI-201 MPS has been found to be a sensitive and objective means of assessing functional regional myocardial perfusion post-operatively<sup>(18)</sup>, and in demonstrating peri-operative infarction and post-operative ischaemia<sup>(19)</sup> as well as residual ischaemia attributable to ungrafted coronary disease<sup>(20)</sup>.

Thus TI-201 MPS has been used as a safe and reliable technique to assess the results of bypass surgery in the postoperative period and can reduce the need for repeated cardiac catheterization in such patients.

#### TI-201 MPS IN PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) PATIENTS.

The first successful percutaneous transluminal coronary artery dilatation was performed in 1977<sup>(20)</sup>. Because of the encouraging results of this new technique for the treatment of severe proximal coronary artery stenosis, it is desirable to have non-invasive methods available to evaluate its effect on regional myocardial perfusion.

Hirzel et al<sup>(22)</sup> have demonstrated the direct relationship between change in size of the vascular lumen and in regional myocardial perfusion as assessed by TI-201 MPS. Similarly Okada et al have documented the improvement in clinical and angiographic factors as well as in myocardial perfusion assessed with TI-201 which occur after PTCA<sup>(23)</sup>. A study conducted by Wijns et al has shown that 4 weeks after primary successful PTCA, abnormal TI-201 scintigraphy in asymptomatic patients was associated with high incidence of restenosis at late angiography (6 months). Thus TI-201 MPS could predict the success of outcome of the intervention<sup>(24)</sup>.

#### TI-201 MPS IN NON-ATHEROSCLEROTIC ANGINAL SYNDROMES.

Although most patients with primary mitral

valve prolapse are asymptomatic, chest pain and arrhythmias are a major clinical manifestation of the symptomatic patient. The problem of differentiating pain due to coronary atherosclerosis from that of mitral valve prolapse without myocardial ischaemia is not entirely solved by exercise ECG, as many patients with mitral valve prolapse have false positive ECG<sup>(25)</sup>. A number of investigators have found normal TL-201 myocardial scans in such patients. They have demonstrated the usefulness of exercise Tl-201 MPS for differentiating patients with primary mitral valve prolapse from those with prolapse secondary to ischaemic heart disease<sup>(25-27)</sup>.

Rubin et al employed Tl-201 MPS to evaluate angina pectoris in patients with idiopathic hypertrophic subaortic stenosis. Stress ECG may not be useful because of electrocardiographic changes of left ventricular hypertrophy in these patients. They found it useful in excluding CAD as a cause of angina in such patients<sup>(28)</sup>.

Tl-201 MPS has also been found to be useful in diagnosing patients with ischaemic cardiomyopathy without past history or ECG suggestion of previous myocardial infarction, and in distinguishing them from those with idiopathic congestive cardiomyopathy.

Fuller et al have demonstrated with Tl-201 MPS the ischaemic effect of exercise induced coronary artery spasm in fully patent arteries and those with only mild luminal plaques. They have thus defined the aetiology of classic anginal pain in patients without significant atherosclerotic coronary disease<sup>(29)</sup>.

Similarly Ahmed et al have shown the role of isolated systolic narrowing of LAD in the absence of significant atherosclerotic disease in chest pain syndromes. Because coronary flow occurs predominantly in diastole, transient systolic narrowing would not be expected to impede flow. However Tl-201 myocardial studies have provided evidence of abnormal myocardial perfusion in such patients<sup>(30)</sup>.

#### OTHER APPLICATIONS OF TL-201 MPS

With the widespread use of this technique numerous other applications of Tl-201 MPS are being reported.

Non-invasive techniques such as ECG and echocardiography have limited value in assessing the severity of right ventricular hypertension in association with chronic airway disease and congenital heart defects. Rabinovitch et al have shown the clinical usefulness of quantitative analysis of Tl-201 myocardial imaging of right ventricular hypertrophy as a screening test for detection of right ventricular hypertension.<sup>(32)</sup>

Additionally Yamazaki et al used Tl-201 MPS to assess non-invasively, regression of right ventricular overload after surgical correction of the condition, and documented continuing decrement of mass and coronary blood flow in the right ventricle upto 3 years after operation<sup>(32)</sup>.

Rey et al determined that Tl-201 MPS could detect myocardial haemochromatosis associated with hypertransfusion therapy in beta-thalassaemia major patients who had no overt cardiac disease<sup>(33)</sup>. Orié et al studied potential kidney transplant recipients with end stage renal disease secondary to juvenile onset diabetes mellitus. They report the high predictive accuracy of Tl-201 MPS for detecting CAD despite low peak heart rate and level of exercise achieved<sup>(34)</sup>.

Felsher et al reported the usefulness of Tl-201 MPS in risk stratification in patients with diabetes mellitus. Patients with abnormal images were found to be at significantly higher risk of future cardiac events than patients with normal images. The exercise ECG response was not a useful prognosticator.<sup>(36)</sup>

#### LIMITATIONS OF TL-201 MPS

As with all other diagnostic techniques, there are certain limitations of Tl-201 MPS.

Myocardial perfusion scans display relative distributions rather than absolute values for myocardial blood flow. In patients with multi-vessel CAD only a single region of myocardium, representing the most severely involved region, may at first become ischaemic during exercise. Symptoms or ECG changes may cause the patient to stop exercising. At this point perfusion abnormalities may be less obvious or non-existent in the other areas and may not be visible on MPS. There is thus a tendency of MPS to identify the most severely ischaemic area among several

that may be present<sup>(36)</sup>. Tl-201 MPS therefore has only limited utility in determining whether or not single, or multivessel disease is present<sup>(37)</sup>.

The distribution of myocardial blood flow within the region of the three major coronary arteries can be assembled from the anterior, left anterior oblique and left lateral myocardial images. Segmental analysis of these three views allows identification of areas highly specific for the individual coronary arteries. However, the correspondence between scintigraphic segments and CAD is not rigorous because the anatomical position of the heart in the chest and the coronary artery distribution vary from patient to patient<sup>(36)</sup>.

## CONCLUSION

Modern medical science is a continuously evolving discipline. In recent years Tl-201 MPS has also been subjected to many advances. New techniques both for data acquisition and data analysis have been developed.

Thus special collimators (multiple pin-hole) and tomographic techniques (single photon emission computed tomography SPECT) have been introduced. Computer methods to quantify Tl-201 uptake and measure Tl-201 washout rates are being more widely used. This has resulted in improved sensitivity of Tl-201 MPS for detecting coronary artery lesions and further enhanced the clinical utility of this valuable diagnostic technique.

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