

Safety and Tolerability of Adenosine Stress Myocardial Perfusion Scintigraphy in the Evaluation of Coronary Artery Disease in the elderly patients- A case control study

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Abstract

Elderly patients referred for evaluation of chest pain are often unable to undertake adequate exercise for exercise stress testing. The aim of this retrospective study was to analyze haemodynamic effects and assess the safety of adenosine stress myocardial perfusion scintigraphy (MPS) in the elderly. Records of 380 Patients (Age range=30-93 years) were reviewed. These were divided into two groups, Group-A with 190 patients who were above 65 years of age and Group-B with 190 patients who were equal or below the age of 65 years, and who had undergone adenosine stress MPS. The two groups were matched for major risk factors and clinical presentations. Symptoms (flushing, headache, chest pain, dyspnoea, neck pain) were recorded throughout the adenosine infusion. Baseline blood pressure, heart rate and ECG were recorded and monitored throughout the study. A total of 167 out of 380 patients (44%) had side effects, 86 of them belonged to Group-A and 81 of them belonged to Group-B. Flushing occurred in 33% of patients in Group-A and 43% of patients in Group-B. Seventeen percent of patients in Group-A had chest pain, while this was encountered in 27% of patients in Group-B. Dyspnoea was recorded in 32% of patients from Group-A, while it was encountered in 21% of patients belonging to Group-B. Neck pain was experienced by 8.4% in Group-A and 15% in Group-B. All of these findings were statistically significant ($p < 0.05$). Several other side effects were also encountered which included headache (Group-A: 14% and Group-B: 21%), abdominal discomfort (Group-A: 19% and Group-B: 23%), Nausea and/or vomiting (Group-A: 4.7% and Group-B: 7.3%). ECG changes were noted in both groups (Group-A: 14% and Group-B: 12%). None of these were found to be statistically significant. Based on this

retrospective study, the authors concluded that Adenosine stress MPS is a safe method for the evaluation of coronary artery disease (CAD) in elderly patients and is well tolerated. Most side effects were less common in those over 65 years of age, except for dyspnoea, which was found to be more common in the elderly than those patients who were less than 65 years of age.

Key Words- coronary artery disease, adenosine, Myocardial Perfusion Scintigraphy (MPS)

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Introduction

The prevalence of coronary artery disease is relatively higher in the elderly as compared to the young. The severity of its manifestations is also much higher in the elderly population (1). Myocardial perfusion scintigraphy (MPS) combined with a treadmill test is the most common nuclear cardiology investigation performed to-day in patients suspected of having coronary artery disease. However, many elderly patients find it rather difficult to complete the tread-mill exercise test due to age-related problems, such as peripheral vascular, neurological, respiratory, renal and joint diseases. In addition, differences in physiological responses to exercise may appear with aging (2-4). Reports suggest that nearly 50% of patients over 75 years of age and 33% of patients below 75 years of age have difficulty in reaching the target heart rate specified in the physical exercise test protocols (5). In such patients pharmacological stress combined with MPS is a logical alternative (6). Pharmacological stress testing has proven to be an excellent alternative to physical exercise testing. Pharmacological stress agents fall into two major categories: coronary vasodilating agents (dipyridamole and adenosine) and inotropic agents (dobutamine and arbutamine). Vasodilators work directly on the coronary vessels to increase blood flow and inotropic agents work indirectly by increasing myocardial work load, which then leads to an increase in coronary blood flow (7, 8). This study was performed to determine if there was any significant change in the safety, haemodynamics or tolerability of adenosine stress myocardial perfusion

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imaging in elderly patients (aged > 65 years) compared to a similar sized group of younger patients matched for major clinical characteristics and risk factors that might influence the safety and feasibility of the test.

Materials and Methods

A retrospective analysis of results of myocardial perfusion studies (using the one day Adenosine stress-rest protocol) done on 380 patients was performed in two groups of patients, Group-A and Group-B. There were 190 patients in Group-A, all of whom were above 65 years of age (Age Range = 66-93 years) who were referred for myocardial perfusion studies during the period 2000-2003. Group-B also consisted of 190 patients, who were either equal to or below 65 years of age (Range = 30-65 years), and were also selected from the patients studied during the same period as Group-A. Patients from both the groups were matched for age, sex and risk factors (hypertension, cholesterol, diabetes smoking, and family history of CAD) (Table 1).

of 750 MBq of Tc-99m tetrofosmin on the same day.

Assessment of signs and symptoms

The systolic and diastolic blood pressure, heart rate and electrocardiograms (ECG) were recorded at the baseline, 90 seconds, 3 minute and 6 minute during infusion and up to 5 minutes during recovery. All symptoms (flushing, headache, chest pain, dyspnoea, neck pain, nausea/vomiting and abdominal discomfort) were recorded throughout the adenosine infusion and during recovery. The presence of any symptoms was sought by direct questioning of the patients normally at 30 second intervals and again at the end of the test as experience has shown that patients may have difficulty in speaking during the actual procedure.

Imaging protocol and SPECT acquisition:

Images were acquired on a triple headed gamma camera (Phillips-Picker, Eindhoven, Netherlands) fitted with low energy general purpose collimators. The Tc-99m tetrofosmin SPECT images were acquired 45 minutes to 1 hour after adenosine infusion and a rest study 4 hours later.

Clinical Features	Group-A (>65 yrs) (n =190)	Group-B (≤ 65 yrs) (n =190)	p value
Age range in years	66-93	30-65	
Men	106	107	0.92
Women	84	83	0.91
History of IHD	52	55	0.68
Previous surgery/PTCA	34	21	0.004*
Hypertension	100	100	1
Diabetes mellitus	52	54	0.78
Smoking	23	30	0.20
Hypercholesterolemia	38	36	0.73
Family history	44	50	0.39

Table 1. Age range, gender and risk factors recorded in both groups of patients (* statistically significant p<0.05)

All patients avoided theophylline and caffeine-containing beverages for 24 hours prior to the study and abstained from food intake for a period of at least two hours before the test. All patients with history of bronchial asthma, severe chronic obstructive pulmonary disease, high-grade atrio-ventricular block and those who had taken caffeine or theophylline within 24 hours of the test were excluded from the test.

Adenosine Stress Test

Adenosine (140µg/kg per minute) was infused using the standard protocol. The one-day stress/rest protocol was used in all patients. At the mid point of the infusion the radiopharmaceutical was injected intravenously (250 MBq of Tc-99m tetrofosmin). The stress images were reviewed immediately after imaging. If they were not unequivocally normal, a rest study was conducted after a further injection

Sixty-four projections (2530 seconds in each) were obtained over a 180° arc. All images were stored in a 128×128 matrix.

Image reconstruction and Reporting:

Tomographic data was reconstructed using iterative reconstruction and smoothed using a count-optimised Wiener filter. Images were re-orientated into the standard short axis, horizontal and vertical long axes for reporting. Images were reported primarily by a single trained reporter but to ensure lack of bias the images were assessed quantitatively using an Emory bull's-eye Plot. A reversible perfusion defect was defined as a perfusion defect on stress images that partially or completely resolved on rest images on both visual analysis and Emory bull's eye plot. A fixed perfusion defect was defined as a perfusion defect on stress images that was also evident on the rest images on both

Haemodynamic and adenosine Stress Test changes	Group-A (>65 yrs) (n =190)	Group-B (65 yrs) (n =190)	p value
Base line heart rate (beats/min)	75±17	77±14	0.81
Heart rate during termination of the test (beats/min)	86±23	91±22	0.60
Base line Systolic BP (mm Hg)	151±30	140±25	0.35
Systolic BP at the end of the test (mm Hg)	137±32	132±27	0.66
Base line Diastolic BP (mm Hg)	80±14	77±14	0.73
Diastolic BP at the end of the test (mm Hg)	73±15	73±14	1
ECG changes	27	23	0.40

Table 2. Changes in ECG and haemodynamic parameters in both groups (A & B) of patients during the Adenosine Stress Test.

Symptoms	Group-A (>65 yrs) (n =190)	Group-B (65 yrs) (n =190)	p Value
Flushing	63(33%)	82(43%)	0.03*
Chest pain/chest discomfort	33(17%)	52(27%)	0.008*
Dyspnoea	61(32%)	41(21%)	0.001*
Headache	14(7.3)	21(11%)	0.12
Abdominal discomfort	19(10%)	23(12%)	0.40
Neck pain	16(8.4%)	29(15%)	0.015*
Nausea/ Vomiting	9(4.7%)	14(7.3%)	0.18

Table 3. Comparison of symptoms during adenosine stress MPS in the two groups of patients (* statistically significant with p value of <0.05)

visual analysis and Emory bull's eye plot.

Statistical analysis:

The patient characteristics, haemodynamics and tolerability were compared using a χ^2 or Student t test as appropriate. A p value of 0.05 was considered significant.

Results

Haemodynamics

The baseline blood pressure was not different with respect to mean systolic (140 ± 25 mm for those in Group-A vs. 151 ± 30 mm Hg for those in Group-B) and diastolic (80 ± 14 vs. 77 ± 14 mm Hg in patients belonging to Group-A and B respectively) blood pressure. There was also no significant change in blood pressure or heart rate during the adenosine infusion. (Table 2).

Tolerability

There were 167 out of 380 (44%) patients, who reported side effects. Eighty six of them belonged to Group-A and 81 to Group-B. This was not significant.

Flushing, chest pain and neck pain were more commonly seen in Group-A than Group-B. This was statistically significant ($p < 0.05$) (Table 3). The most common of these was flushing, with over a third of patients suffering from this side effect. Chest pain and discomfort and neck pain occurred in about a quarter to a fifth of all patients. Two patients under 65 years of age (Group-B) needed treatment

of their chest pain with GTN. Unlike dipyridamole infusions where headache is almost inevitable, the number of patients suffering from headache was low. This was observed more commonly in the younger age group. Abdominal discomfort, normally presenting as a cramping pain, was also not common but again occurred slightly more frequently in the younger age group.

The other common symptom in our patients was dyspnoea. One third of patients in Group-A and one fifth of patients in Group-B suffered from this symptom.

With regard to the haemodynamic changes following adenosine, no significant differences were noted with regard to changes in pulse rate and blood pressure in the two groups. Likewise there was no significant difference with regard to changes in the ECG patterns between the two groups.

MPS-SPECT results

A total of 240 out of 380 (63%) patients had abnormal scans on quantification. In Group-A there were 126/190 (66%) abnormal studies. This compares well with 114 abnormal studies (60%) in Group-B. This difference was not significant. There was also no significant difference in the gender distribution of abnormal myocardial scans in this study. In both age groups abnormal studies were seen predominantly in men. In Group-A, 82/106 (77%) men and 44/84 (52%) women had abnormal studies; while in Group-B, 82/109 (75%) men and 32/81 (39%) women had

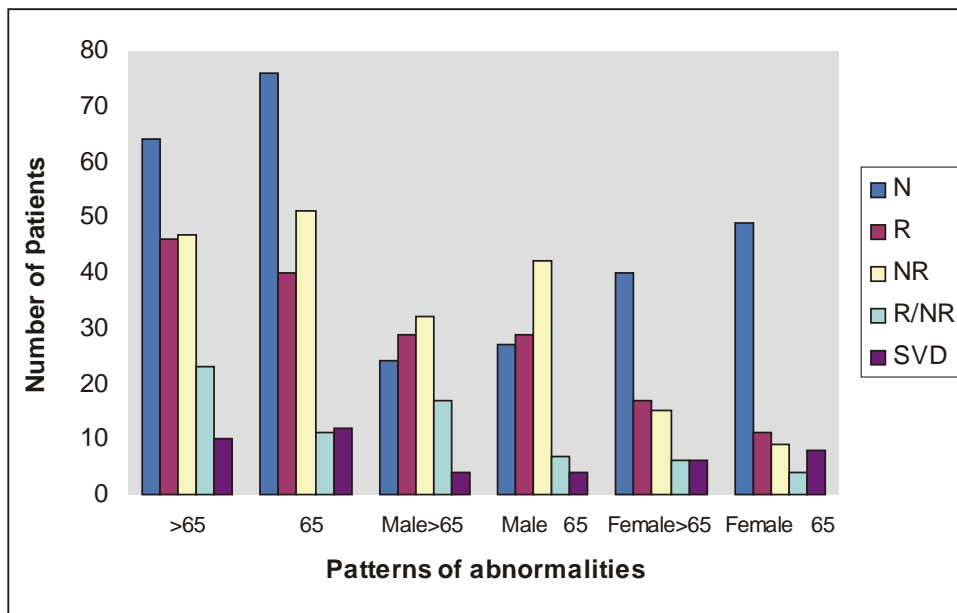


Figure1. The patterns of perfusion abnormalities in the two groups of patients (Group-A: >65 years and Group-B: ≤ 65 years)

(Note abbreviations: N=normal scan, R=reversible ischemia, NR=non-reversible ischemia, R/NR= combination of reversible and non reversible defects, SVD=small vessel disease)

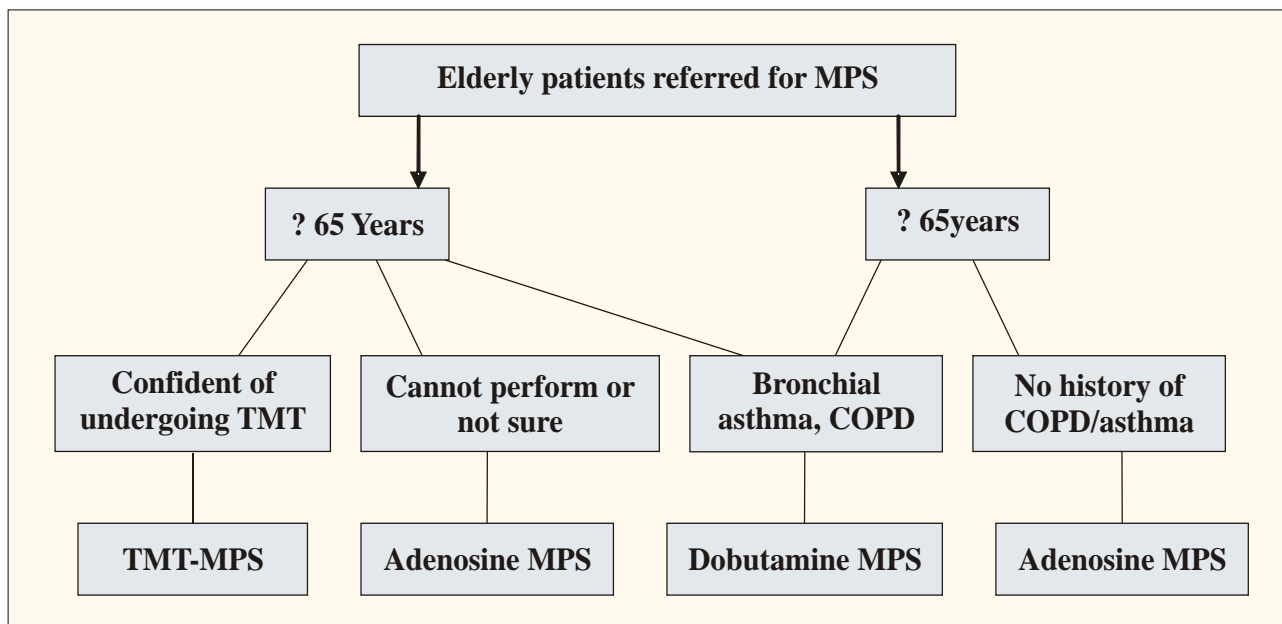


Figure 2. A proposed algorithm for elderly patients, referred for Myocardial Perfusion Scintigraphy

abnormal studies (Figure 1). With regard to abnormalities in women, 52% women had abnormal myocardial perfusion scans in Group-A, as compared to 39% in Group-B. This was found to be statistically significant ($p < 0.05$).

Discussion

Our study confirms the previous reports in literature about the high incidence of side effects in pharmacological adenosine stress testing (9). However, it may be noted that the side effects were only transient, minor in severity and

rarely required additional medical intervention. It may also be noted that in our study groups only less than 1% of patients required any medical intervention. It was also observed that advanced age was not the determinant of the increasing rates of side effects, except for dyspnoea during the test, which was found to be significantly higher in the elderly population (Group-A) than in younger population (Group-B). However, each episodes of breathlessness lasted for only a few minutes and none of the patients required any additional or supportive treatment. Further, contrary to general belief, the younger patients under the

age of 65 years (Group-B) experienced the highest rates of chest pain, neck pain and flushing in our study, compared to relatively older patients in Group-A.

Pharmacological stress with vasodilators alters the myocardial blood flow through the coronary arteries and causes differential dilation of the normal and stenosed coronary arteries (10-12). These agents do not generally produce ischemia and hence they are being used more frequently in pharmacological stress radionuclide MPS in preference to ionotropic agents; especially in those patients who belong to high risk categories (7) (Figure 2).

Our study did not show any significant difference in the number of patients having abnormal myocardial perfusion scans between the two groups. However as expected the rate of abnormal scans in younger women (Group-B) is significantly lower than that in women above the age of 65 years (Group-A). The rate of abnormal studies in men in both the groups was found to be similar.

A treadmill test in the elderly patients provides a useful insight into the maximum capacity of an individual to augment cardiac and peripheral vascular function and the mechanisms involved in this process. However, their relevance is not directly applicable to the usual aerobic activities of everyday living, which are typically sub maximal (3). Many patients are however unable to complete any meaningful exercise (5).

Exercise or dobutamine alone produces less increase in myocardial blood flow than either dipyridamole or adenosine (13-16). Hence, dobutamine is considered less effective as a pharmacological stress agent for detecting coronary artery disease (9). Elderly patients are at a higher risk for developing spontaneous and exercise-induced arrhythmias (17-19) as well as impairment of compensatory mechanisms for hypotension. Therefore, these patients may be more vulnerable to hypotension and arrhythmias during a dobutamine stress test. Dobutamine in combination with atropine is considered to be as effective as dipyridamole for producing myocardial hyperaemia (20) but it has not been validated in elderly patients. A higher prevalence of supraventricular tachycardia, atrial fibrillation and ventricular tachycardia has been reported with Dobutamine in the elderly (6).

The recovery time in adenosine is only 3-5 minutes as the half-life of adenosine is only 20 seconds. The "adenoscan multicenter trial" with 9,256 participants has concluded that adenosine infusion is safe and vasodilator side effects are generally well tolerated irrespective of age (21). The results of our present study support the findings of the multi-centre study. Further, it may be noted that the results were not stratified by age in the adenosine multi-centre study, as in the present study. The purpose of the large adenosine multi-centre study (21) was to determine the safety of adenosine infusion. The infusion protocol was completed in 80% of patients, dose reduction was required in 13% and the infusion was terminated early in 7% of patients. About 0.8% of patients required aminophylline.

The multi-centre study also reported minor and well-tolerated side effects in 81.1% of patients, which is slightly higher than the present study. Transient atrio-ventricular (AV) node blockade occurred in 706 patients and resolved spontaneously in most patients without alteration in the adenosine infusion (21). The results of our study are comparable with the results of the multi-centre study in terms of safety and efficacy even in the elderly patients, with our figures suggesting a similar rate of overall side effects but with less severity. This difference in severity may be due to a relatively smaller sample size of our study, or could be due to a completely different patient population demographically. These things need further clarification in the future.

Conclusion

Adenosine has a good safety profile. When combined with MPS, adenosine is an effective method for the diagnosis, risk stratification, treatment and follow-up of elderly patients with coronary artery disease. Pharmacological stress testing with adenosine has become an indispensable tool for radionuclide myocardial perfusion imaging studies in the elderly.

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