

# The comparison of two gated SPET protocols: adenosine Tc-99m tetrofosmin and treadmill exercise Tc-99m MIBI

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## Abstract

**BACKGROUND:** The effect of adenosine and exercise on gated SPET left ventricular ejection fraction (LVEF), end diastolic volume (EDV) and end systolic volume (ESV) has not been fully investigated. The aim of the study was to compare functional measurements obtained in one-day adenosine rest and two-day stress-rest protocols in relation to ischaemia.

**MATERIAL AND METHODS:** Out of 226 consecutive patients examined with submaximal treadmill stress-rest 700 MBq Tc-99m MIBI, 26 were chosen to match those subjected to adenosine (140 µg/kg/min) enhanced by a low level exercise protocol (300 MBq and 700 MBq Tc-99m tetrofosmin for stress and rest respectively). All images were acquired on a double head system and were gated using 8 frames, 25 s per frame.

**RESULTS:** ED and ES volumes increased after adenosine but decreased after treadmill resulting in the post-stress LVEF being significantly greater than after adenosine,  $60 \pm 11$  v.  $51 \pm 13\%$  ( $p < 0.01$ ). This was caused by the smaller post-stress ESV in the treadmill group  $40 \pm 20$  v.  $51 \pm 34$ ,  $p < 0.05$ . In non-ischaemic scans the LVEF was greater ( $61 \pm 8$  v.  $51 \pm 14$ ,  $p < 0.01$ ) and EDV and ESV smaller after both stress and rest.

**CONCLUSIONS:** The adenosine test may have an opposite influence on the EDV and ESV in comparison to the submaximal treadmill test and therefore the left ventricular function measurements after adenosine infusion should be interpreted carefully and may not represent those acquired after physical exercise. In the gated SPET scans showing ischaemia the post-stress EDV and ESV may be greater and the LVEF lower than at rest.

**Key words:** gated SPET, adenosine, exercise, left ventricular function

## Introduction

Gated single photon emission tomography (GSPET) imaging was developed in the late 1980s [1]. It allows simultaneous assessment of perfusion and function of the left ventricle with a single injection of myocardial perfusion radiopharmaceutical. There are several perfusion tracers used in gated SPET, most of them Tc-99m labelled, such as MIBI (metoxyisobutylisonitrile) or tetrofosmin, which provide high count density and relatively stable myocardial distribution [2, 3]. Liver uptake of Tc-99m MIBI is high though hepatobiliary clearance is relatively rapid. Hepatic and bowel activity present at 1 hour post injection may obscure the inferior myocardium. After stress injection, the heart-liver ratio is higher than 1:1 immediately after stress injection and progressively increases over the next 3 hours. After rest injection, the initial heart-liver ratio is 1:2 and progressively increases so that by 2 hours the ratio is 1:1. The extraction fraction of tetrofosmin is lower but the liver and gall bladder uptake are not as prominent as with Tc-99m MIBI. The dissimilarities, however, are subtle and considered not clinically significant [4].

Single day vasodilator, inotropic agent or exercise with Tc-99m radiopharmaceutical are commonly used protocols for myocardial perfusion evaluation. However some laboratories still prefer two separate days for stress or vasodilatation and rest studies. The differences between adenosine and exercise stress gated SPET study protocols may affect left ventricular ejection fraction (LVEF), end diastolic volume (EDV) and end systolic volume (ESV) values. The aim of the study was to compare gated SPET left ventricular function measurements obtained in two different

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protocols: one-day adenosine rest and two-day stress-rest in relation to ischaemia.

## Material and methods

Twenty-six randomly chosen patients successfully underwent a same-day adenosine stress-rest sequence for the assessment of both myocardial perfusion and left ventricular function with a gated SPET perfusion imaging technique (Fig. 1A). The studied group consisted of 16 men and 10 women. Five of them had a history of non-recent myocardial infarction (2 anterior, 2 inferior and 1 lateral). The mean age and weight were  $61 \pm 6.7$  years and  $78.7 \pm 14.3$  kg respectively. The infusion of adenosine ( $140 \mu\text{g}/\text{kg}/\text{min}$ ) was 6 minutes long with the stress dose of 300 MBq of  $^{99\text{m}}\text{Tc}$  perfusion tracer-tetrofosmin- $^{99\text{m}}\text{Tc}$  Myoview (Nycomed Amersham Healthcare, London, United Kingdom) administered after 3 minutes. The infusion was combined with a low-level physical exercise on cycloergometer. Four patients presented with left bundle branch block in ECG and they were not subjected to exercise. Every patient was reinjected with 700 MBq of  $^{99\text{m}}\text{Tc}$  Myoview after 3–4 hours. At the time of reinjection the glyceryl trinitrate spray dose was administered sublingually. For the stress portion of the examination, images were obtained approximately 45 minutes after injection. For the resting studies, images were obtained 30 minutes after injection.

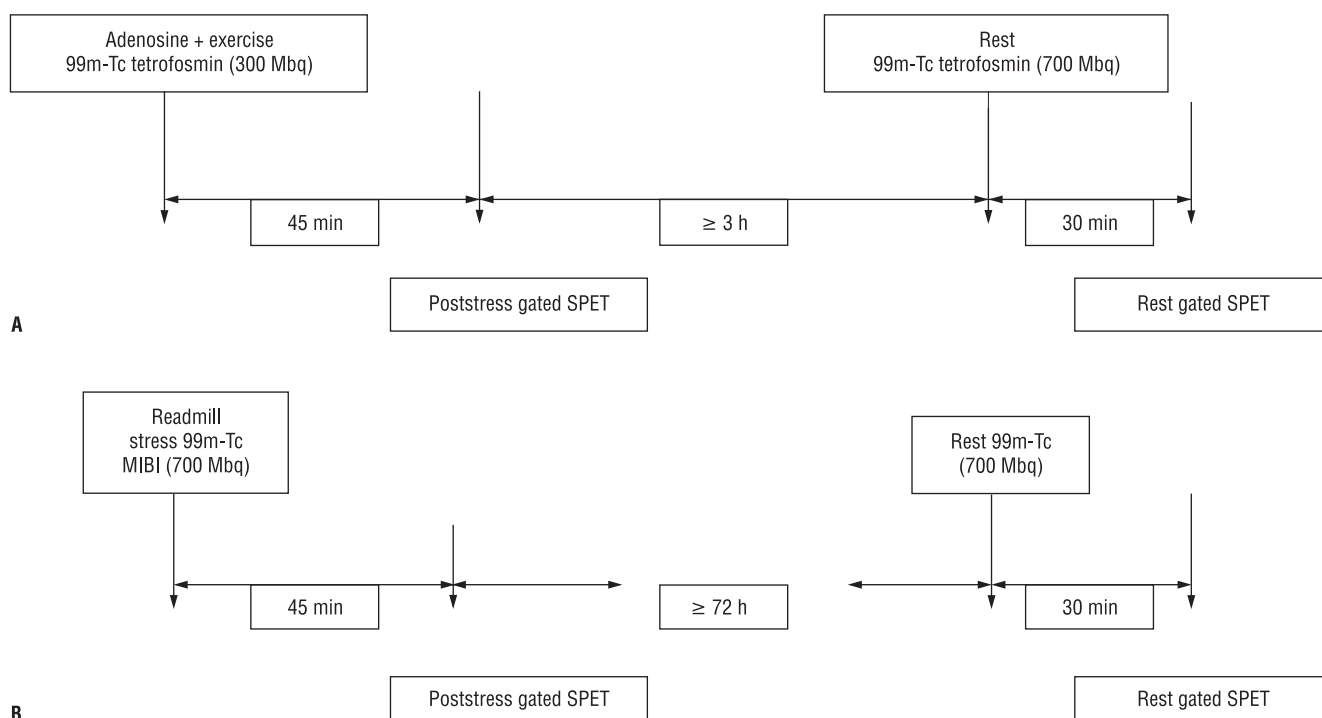
Two hundred and twenty-six consecutive patients were examined by means of two-day stress rest protocol depicted in Figure 1B. The patients were subjected to submaximal symptom limited exercise on a treadmill and the Tc-99m MIBI (metoxyisobutylisonitrite, Polatom, Otwock Swierk, Poland) was injected at peak heart rate (at least 85% of age predicted) and the patient was asked to

continue for 1 more minute. After completing the exercise the patient was asked to have a dairy meal to promote the hepatobiliary clearance. The acquisition started 45 minutes to 1 hour after the exercise. On a separate day the rest study was performed with similar time sequence.

Twenty-six subjects from the treadmill protocol group with the same characteristics: age, sex, weight, prior myocardial infarction, pre-test probability, rest LVEF and rest EDV, were selected to clinically match the patients from the adenosine group.

Both post-stress and rest perfusion SPET studies were gated using 8 frames for the cardiac cycle with the window of acceptance RR interval difference of  $\pm 50\%$ . SPET images were obtained over a  $180^\circ$  circular orbit by using a dual-head detector gamma camera Varicam (Elscont, Haifa, Israel) equipped with high-resolution collimators and the detectors placed at right angles. Images were obtained with 60 ( $30 \times 2$  heads) projections at 30 seconds both for stress and rest. The camera was set for a 140-keV photopeak with a 20% window. Images were obtained with a matrix size of  $64 \times 64 \times 8$ . The projection data were prefiltered with a two-dimensional Butterworth filter (order 5). Images were reconstructed with filtered back-projection and no attenuation correction. After reconstruction of the transverse images, the short-axis images underwent pre-processing for gated left ventricular ejection fraction (LVEF) quantification by using previously validated Quantitative Gated SPET (QGS) software [5] using the Xpert processing station (Elscont).

The summed perfusion data set was then transferred to the Hermes Processing Station (Nuclear Diagnostic, Sweden) for perfusion interpretation. The perfusion data set was processed for qualitative interpretation of the perfusion images by using a two-dimensional Wiener filter with a frequency of 5.0 with 0.35 cycles



**Figure 1.** Protocols and timeframes used in treadmill exercise Tc-99m MIBI group — **A** and adenosine vasodilatation with Tc-99m tetrofosmin — **B**.

per pixel with further reconstruction and reorientation in the short, vertical, and horizontal long axes. Resting and post-stress tomograms were qualitatively analysed in particular myocardial walls (anterior, lateral, inferior, septum) and apex. Each of the summed resting and stress studies was arbitrarily evaluated for the presence of significant reversible myocardial ischaemia.

The baseline characteristics of the population study are given as the mean  $\pm$  standard deviation for continuous variables in the interval scale. The Student t-test was applied for continuous data, such as left ventricular ejection fraction, end diastolic and end systolic volumes. The logistic regression model was used to assess the predictive value of the differences between left ventricular measurements obtained at rest and after stress for the prediction of the likelihood of ischaemia. A p value of less than 0.05 was considered to indicate a statistically significant difference for all variables compared.

## Results and discussion

The findings in both groups are presented in Table 1. The end diastolic (EDV) and end systolic (ESV) volumes increased significantly ( $p < 0.05$ ) after adenosine causing the LVEF post adenosine to be diminished in comparison to rest. In contrast to the above, the treadmill stress slightly increased post exercise LVEF ( $p = \text{NS}$ ). This resulted in the treadmill stress LVEF being significantly greater than in adenosine group  $60 \pm 11$  v.  $51 \pm 13\%$  ( $p < 0.01$ ). The above was caused predominantly by the post-stress end systolic volume being significantly smaller in the treadmill group  $40 \pm 20$  v.  $51 \pm 34$ ,  $p < 0.05$ .

In both groups the perfusion evaluation showed significant reversible myocardial ischaemia in 14 cases. Twelve scans from the adenosine group showed normal perfusion at stress and rest and so did 11 studies from the treadmill group. In one study a persistent defect was found in the inferior wall, consistent with

the prior history of inferior myocardial infarction. In negative scans the gated SPET analysis showed greater LVEF ( $61 \pm 8$  v.  $51 \pm 14$ ,  $p < 0.01$ ) and smaller ED and ES volumes both after stress and at rest (Table 2). The EDV and ESV values were larger in positive perfusion scans independently of the stress protocol used. The latter findings may be due to a higher proportion of male patients having reversibility and therefore larger hearts in this group.

In order to find the relationship between the gated SPET quantitative results and positive myocardial perfusion report, we assessed the predictive value of the change in left ventricle measurements for estimating the likelihood of ischaemia with a logistic regression model. The decrease in the post-stress LVEF compared with the LVEF at rest together with the changes in end-diastolic and systolic volumes were associated with the increased likelihood of ischaemic perfusion scan pattern with a  $\chi^2$  value of 9.30 ( $p = 0.0255$ ,  $df = 3$ ). None of the above differences was a good predictor alone, with the EDV difference being the most powerful but not statistically significant ( $p = 0.06$ ,  $df = 1$ ).

From the standpoint of defect contrast and optimal image quality, the two-day protocol is ideal [6]. The 2-day stress-rest protocol is often not convenient for patients; therefore, most laboratories perform the low-dose and high-dose same-day protocol [7]. There is a variety of protocols of single-day myocardial perfusion stress test. Because of the higher amount of radioactivity administered at rest with a single-day imaging protocol by using a rest-stress  $^{99m}\text{Tc}$  radiopharmaceutical study usually post-stress tomograms are gated, with the assumption that they reflect resting function. However in departments where a single day stress-rest protocol is routinely used, the higher activity is administered at rest, giving the true rest function.

Ideally both sets of tomograms should be gated in order to identify wall motion abnormality. Wall motion disturbances that occur on the post-stress images but are not seen on rest ones imply the presence of myocardial stunning and are highly specific

**Table 1. Findings of quantitative gated SPET analysis in adenosine and treadmill groups**

	Adenosine* Tc-99m tetrofosmin	Exercise** Tc-99m MIBI	p
LVEF stress (%)	$51 \pm 13$	$60 \pm 11$	$< 0.01$
LVEF rest (%)	$56 \pm 11$	$57 \pm 11$	NS
EDV stress [ml]	$97 \pm 50$	$88 \pm 36$	NS
EDV rest [ml]	$91 \pm 46$	$93 \pm 36$	NS
ESV stress [ml]	$51 \pm 34$	$40 \pm 20$	$< 0.05$
ESV rest [ml]	$43 \pm 32$	$41 \pm 30$	NS

\*All changes between stress and rest were statistically significant,  $p < 0.05$ , \*\*the differences between stress and rest were not significant,  $p = \text{NS}$

**Table 2. Left ventricular parameters in patients with and without reversible ischaemia**

	Ischaemic patients (n = 28)	Non-ischaemic patients (n = 24)	p
LVEF poststress (%)	$51 \pm 14$	$61 \pm 8.4$	$< 0.01$
LVEF rest (%)	$55 \pm 13$	$62 \pm 7.0$	$< 0.03$
EDV poststress [ml]	$104 \pm 63$	$75 \pm 20$	$< 0.05$
EDV rest [ml]	$106 \pm 58$	$73 \pm 24$	$< 0.02$
ESV poststress [ml]	$56 \pm 55$	$30 \pm 14$	$< 0.04$
ESV rest [ml]	$52 \pm 50$	$28 \pm 13$	$< 0.04$

for the presence of coronary artery disease. Other helpful parameters are wall thickening and discrete wall motion changes, being indicators of the presence of severe coronary stenosis [6].

It has been documented that adenosine and exercise myocardial perfusion SPECT studies provide similar information about the perfusion both with Tc-99m. MIBI and tetrofosmin [8, 9]. We found several substantial differences between adenosine and exercise groups during our comparison. In the paper of Bavelaar-Croon et al. [10], the authors analysed the gated SPET functional measurements and they did not find any differences with regard to ejection fraction between adenosine and exercise.

Myocardial perfusion imaging and finding a perfusion defect is based on the concept of inhomogeneous blood flow between the areas supplied with stenosed and non-stenosed vessels during the state of hyperaemia [4]. Exercise is the oldest stress modality, the most physiological and possessing favourable flow v. tracer uptake characteristics. In addition exercise stress has a very important interaction with nuclear cardiac imaging. During exercise the liver uptake markedly decreases. When the liver uptake is high, such as during pharmacological stress or at rest, the proximity between the liver and the heart may compromise the interpretation of the Tc-99m radiopharmaceuticals [6].

Pharmacological stress or vasodilatation (i.e. adenosine) is frequently used especially for patients unable to perform an exercise stress test or with contraindications to exercise. However the pharmacologically induced coronary vasodilatation is not a "stress" test. It only slightly increases the rate and pressure product and cardiac output up to 50%. The ischaemia is only present in a minority of studies due to the coronary steal [11]. However even during exercise treadmill stress test the ischaemia is not necessary to visualise the perfusion defect. The disparity of the flow makes the myocardial perfusion scanning such a sensitive tool [4].

Therefore it is difficult to suspect that myocardial stunning happens after the exercise and almost improbable during adenosine infusion, even combined with low level physical exercise. Nonetheless during exercise the rate and pressure product increases significantly and the ischaemia, if it happens, may cause abnormal thickening and abnormal wall motion. The wall motion abnormality may persist for up to 2 hours after the ischaemic event [12, 13].

The changes observed in our study in left ventricle function after adenosine are probably related to prolonged haemodynamic effect of adenosine. In contrast to our findings, Ogilby et al. [14] did not find substantial changes in left ventricular end-diastolic volume and ejection fraction. Others, however, have measured a slight increase in end-diastolic volume [15].

There are not enough data regarding the comparison of gated SPECT after adenosine and exercise. The obvious limitation of our study is that the study protocols were not performed in the same subjects but in clinically matched ones. The possible individual differences in response to stress protocols between subjects were unavoidable and may influence the results. The head-to-head comparison should give more adequate answers about the differences between adenosine and exercise gated SPET.

It had been suggested that adenosine has a negative indirect inotropic effect or antiadrenergic effect [4]. To date our report is the first documenting this in humans. In the present study only in the adenosine group did we find significant differences between stress and rest studies as far as the LVEF is concerned.

Borges-Neto et al. [16] documented persistent functional abnormalities after an episode of acute ischaemia. One of the potential technical explanations for their findings (rather than a true physiological phenomenon) is the presence of severe perfusion abnormalities and the problems with the edge detection algorithm in finding the correct endocardial border because of the presence of decreased counts. The edge detection algorithm used was the same as in our study, originally described by Germano et al. [5], which identifies perfusion in underperfused areas of the myocardium by extracting count profiles from the non-threshold image. Despite the predominant perfusion abnormality in the endocardium during ischaemia, some degree of myocardial perfusion is always seen in the epicardium and detected in the count profiles. Furthermore, an asymmetric Gaussian curve is fitted to each profile, and the inner and outer SDs of the curve are measured. When perfusion is severely depressed along a profile, these SDs are combined with those of each of its four spatial neighbouring profiles. The algorithm described above may need specific correction for low count data sets in order to give a reliable result.

Similarly to others [16] we noted statistically significant differences of the changes of left ventricular functional parameters between resting and post-stress measurements when patients with and without ischaemia were considered. Borges-Neto et al. [16] found that the change in ejection fraction between stress and rest was a moderately good predictor of ischaemic scan. Our findings show that only the combination of changes of LVEF, end-systolic and end-diastolic volumes were associated with reversible ischaemia. In the present study the exercise stress test and the adenosine infusion having various effects on the LVEF were used, so our setting requires more cases to improve the statistical power.

Conversely in a more recent study by Bavelaar-Croon et al. [10] no significant differences between post-stress and rest LVEF were observed in patients after myocardial infarction with ischaemia in comparison to control group. The dissimilarities may result from the different method and patient population.

## Conclusions

The adenosine stress test may have an opposite influence on the EDV and ESV in comparison to the submaximal treadmill stress test and therefore the left ventricular function measurements after adenosine infusion should be interpreted carefully because they may not represent those acquired after physical exercise. In the gated SPET myocardial perfusion scans showing ischaemia may be associated with the post-stress end-diastolic and end-systolic volumes greater and the ejection fraction lower than at rest.

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