The effect of separate and combined visual evaluation of imaging performed in supine and prone positions in $^{99m}$Tc-methoxy-isobutyl-isonitrile (MIBI) myocardial perfusion stress study on the need for rest study in men without a known history of coronary artery disease.

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**Introduction:**

$^{99m}$Tc-methoxy-isobutyl-isonitrile myocardial perfusion imaging ($^{99m}$Tc-MIBI MPI), is the most commonly used noninvasive stress imaging method for the diagnosis of coronary artery disease (CAD) (J1). However, despite its overall effectiveness, the interpretation of MPI is complex due to potential imaging artifacts, including those related to the patient and equipment (J). Soft tissue attenuation, such as that caused by breast position or the diaphragm, is one of the most common factors that can reduce the test accuracy for detecting CAD and affect image quality. (G4). To reduce the factors that decrease quality, methods such as electrocardiography-gated imaging, attenuation correction software, and changing the patient’s position have been proposed (G4, G5). MPI is conventionally performed in the supine position (Y). However, different positions are now being used to achieve better imaging quality (G).

One approach that has been reported to improve the diagnostic accuracy of MPI is the use of a supine-prone combination rather than supine MPI alone (C).

In recent years, numerous studies have shown significant reductions in both diagnostic performance and patient radiation exposure when using "stress-first" imaging, such that a normal stress study can eliminate the need for subsequent rest imaging (A31, A32, A33, A34). The normal stress study will eliminate the need for subsequent rest imaging, thereby reducing the examination time, radiation dose, and the doses of radiopharmaceuticals used.

In cases of diaphragmatic or breast attenuation, the absence of perfusion defects in stress-prone imaging can help exclude ischemic heart disease, especially when combined with a supine study, thereby reducing the need for rest imaging (O).

It has been reported that the addition of prone MPI to supine MPI increases the diagnostic accuracy in populations consisting of both women and men (C6, C7, C8). However, data directly comparing these two imaging strategies, especially in cohorts consisting solely of men, are limited (C).

Despite its potential to increase diagnostic accuracy, the combined supine-prone MPI is not widely utilized.

In our study, we retrospectively investigated the effect of stress supine-only, stress prone-only, and combined stress supine-prone MPS studies on the need for rest imaging in male patients without known coronary artery disease in whom there is limited data in the literature.
Methods:

Patients Population:

In this retrospective study, we included 378 male patients older than 18 years of age without known CAD who underwent stress MPI in supine and prone positions between December 2020 and June 2022 in our clinic and whose files and MPS images were available. Women, patients younger than 18 years of age, patients with known coronary artery disease, and patients whose follow-ups were not available were excluded.

Institutional ethics committee approval was obtained for this retrospective study. The study was conducted by the principles outlined in the Helsinki Declaration of 1964 regarding biomedical research involving human subjects. Informed consent was not obtained due to the retrospective nature of the study.

Patient Preparation, Exertional Stress/Pharmacologic Stress Protocols:

The patients were instructed to refrain from consuming nicotine or caffeine-containing beverages for 12 hours and to discontinue taking persantine 24 hours before the screening. They were informed about the discontinuation of nitrate, beta blocker, and calcium antagonist medications based on their half-lives. Before the radionuclide study, all patients had fasted for at least 4 hours. We implemented the procedural guidelines of the European Association of Nuclear Medicine (EANM) for radionuclide myocardial perfusion imaging protocol (Z). We followed the one-day stress-optional-rest protocol. For the initial injection, a dose of 250-400 MBq of radiopharmaceutical was administered, while for the second injection, three times more radiopharmaceutical was administered. The stress treadmill test was performed using the Bruce/modified Bruce protocol. The radiopharmaceutical injection was administered when the target heart rate reached a minimum of 85%. Afterward, the exercise was continued for at least 1-2 minutes before being terminated. Dipyridamole was used for pharmacological stress. Dipiridamole was continuously infused at a rate of 140 μg/kg/min for a duration of 4 minutes, and the radiopharmaceutical was injected 3-5 minutes after the completion of the dipyridamol infusion.

Imaging Protocol:

We performed imaging on a Siemens symia E gamma camera (Hoffman Estates, IL, USA) with a LEHR collimator. The shots were taken with a 64x64 matrix, in 16 projections, with each image for 20 seconds. Detectors moved on a 180° arc from 45° right anterior oblique to 45° left posterior oblique. The zooming factor was 1.45. Images were reconstructed using a back projection algorithm and a Butterworth filter with a cutoff frequency of 0.45 cycles per pixel and order 5.

The imaging was initiated 15-45 minutes after the radiopharmaceutical injection. The patients were initially scanned in the supine position with their arms above their heads. They were then scanned in the prone position with their arms extended forward. The patient’s chest was positioned near the SPECT detectors, ensuring that the heart was within the center of the field of view. After evaluating the supine and prone images, patients who were determined to require rest imaging underwent a subsequent radiopharmaceutical injection. The images were evaluated using the Siemens Syngo.via MI apps program (Erlangen, Germany).

Image analysis: We used a 17-segment myocardial map for semiquantitative visual assessment. We coded according to which coronary vessel territory supplied the corresponding myocardial segment (Z1)

Two different evaluators assessed the images. Evaluator 1 first evaluated the supine image alone (Supine1) and noted whether rest imaging was required/not required. At a different time, he assessed the prone image alone (Prone1) and noted rest imaging was required/not required. He then evaluated the supine and prone images together at different times (supine1+prone1). He noted whether rest imaging was necessary or not. The same process was followed for evaluator 2 (supine2, prone2, supine+prone2). If neither supine nor prone image was judged to have a perfusion defect, it was coded as no defect (no need for rest imaging). If a defect was seen in only one of the supine or prone images and no defect was seen in the other image, it was coded as no defect (no need for rest imaging) (Figure 1).
If a defect was seen in both supine and prone images, supine+prone images were evaluated together; a) if the perfusion defect originated from different vessel regions (e.g., RCA region in supine image, LAD region in prone image), it was interpreted as a mismatch defect and coded as no need for rest imaging; b) if the perfusion defect originated from the same segment(s), it was interpreted as a match defect and coded as need for rest imaging (Z).

We performed a cohen's-kappa agreement analysis between the supine+prone assessment results of both evaluators. We observed strong agreement between the final results of the two assessors (Kappa =0.846, p<0.001). Therefore, we accepted the supine+prone evaluation result as the reference standard. Our image evaluation algorithm is shown in Figure 3.

**Statistical analysis**

Statistical analyses were performed with IBM SPSS Statistics, Version 23.0 (SPSS Inc., Chicago, USA) and MedCalc® Statistical Software version 22.009 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023). Variables belonging to the groups were reported as n (%) and standard deviation according to data types. The distribution of dichotomized data between groups was evaluated by the Chi-square test. Pearson Chi-Square or Fisher’s Exact Test p values were used for significance considering the number of patients in the categories. Kappa analysis was used for inter-evaluator agreement. For performance measures, ROC Curve analyses were performed to measure sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. The significance limit was accepted as p < 0.05.

**Results:**

We analyzed 378 male patients (mean age 56.47 ± 12.940) with stress supine and prone imaging. We applied pharmacologic stress in 287 patients (75.9%) and exertional stress in 67 patients (24.1%).

**Evaluator 1:**

Supine1 decided on the need for a rest study in 230 patients (60.8%). In 150 patients (65.2%) it made a false positive decision. The false positivity of supine1 was 33.4%. Prone1 decided to rest in 204 patients (54%). It gave a false positive decision in 124 (60.8%) patients. The false positive rate of prone1 was 29.4%.

With supine1+prone1 evaluation (number of patients with actual need for rest study), rest was decided in 80 patients (21.2%). In 76 (33%) of 230 patients in whom supine1 decided to rest, prone1 said no need for rest (Corrected). In 50 (24.5%) of 204 patients in whom prone1 decided to rest, supine1 said no need for rest. Supine1+prone1 assessment reduced the need for rest by 65% compared with supine1 and 60% compared with prone1.

**Evaluator 2:**

Supine2 made a rest work needed decision in 193 patients (51.1%). In 118 patients (61.1%) it gave a false positive decision. The false positivity of supine2 was 28%. Prone2 decided to rest in 202 patients (53.9%). It gave a false positive decision in 127 patients (62.9%). The false positive rate of prone2 was 29.7%.

With supine2+prone2 evaluation (number of patients with actual need for rest study), rest was decided in 75 patients (19.8%). In 63 (32.6%) of 193 patients in whom supine2 decided to rest, prone2 said no rest was needed (Corrected). In 72 (35.6%) of 202 patients in whom prone2 decided to rest, supine2 said no need for rest. Supine2+prone2 reduced the need for rest by 60.4% compared to supine1 and 62.8% compared to prone1.

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy results of the evaluators in deciding the need for rest are given in Table 1.

The need for rest was significantly more likely to originate from the RCA (inferior wall) region by evaluators 1 and 2 based on supine+prone images.

The information on which vascular territory the need for rest originated from is given in Table 2.
False positive rates were higher in favor of RCA in the supine evaluation compared to the prone evaluation. False positive rates at the LAD site were higher in prone imaging than in supine imaging. False positive rates in the LAD and RCA sites were similar in the prone imaging.

False positive rates are given in Table 3.

**Intra-evaluator Agreement:** There was a low-level agreement between supine 1 and prone 1, supine1 and supine1+prone1, and prone 1 and supine1+prone1. We also observed low agreement between supine 2 and prone 2, supine2 and supine2+prone2, and prone 2 and supine+prone2.

**Inter-evaluator Agreement:** We observed moderate to strong agreement between supine1 and supine 2, between prone 1 and prone 2, and between supine1+prone1 and supine2+prone2.

Intra-evaluator and interevaluator agreement in rest decision-making is given in Table 4.

**Follow-up**

80 patients underwent rest imaging. In 36 patients, stress and rest images were evaluated together and it was concluded that there was no perfusion defect. Coronary angiography was performed in the remaining 44 patients. 5 patients had no stenosis, 15 patients had less than 50% stenosis and medical follow-up was recommended, 13 patients had 50-99% occlusion and stenting was performed, 5 patients underwent by-pass due to total occlusion, 1 patient had a muscular bridge, 2 patients had slow flow in the LAD, and the information of 3 patients was not available. There was no cardiac or noncardiac death.

**Discussion**

MPI is known to have a negative predictive accuracy to rule out ischemic heart disease and future cardiac events (O12 ). However, to improve the accuracy of scintigraphic evaluation, it is necessary to distinguish between artifacts and true perfusion abnormalities.

Combined supine-prone myocardial perfusion imaging has been shown to reduce artifacts compared with supine-only MPI in mixed-sex populations with different risks for coronary artery disease, with patients often serving as their controls. However, direct comparison of these imaging strategies in men is limited (C).

Arsanjani et al. reported that in a mixed-sex population, combined supine/prone imaging improved specificity and accuracy compared to supine imaging alone, and Nishina et al. reported that combined supine-prone stress imaging had higher specificity than prone or supine imaging alone. (J, Y)

Taasan et al. reported that the use of combined supine-prone MPI reduced the rate of suspicious interpretations from 18% to 4%, and Gutstein et al. reported that pron imaging reduced the rate of suspicious scans from 40.7% to 15.4% and the rate of ischemic studies from 34.1% to 7.7%. (N, C)

In the study by Ceylan et al., prone imaging eliminated the need for rest perfusion study in 76 of 98 patients (77.5%). In 76 (85.4%) of the patients reported as normal (n=89), there was no need to perform resting perfusion studies thanks to pron study results. (O).

Our study differs from studies conducted on mixed-gender populations, was conducted only on male patients, and for both observers, visual assessment alone eliminated the need for resting study in at least 60% of the patients, thanks to the combined supine-prone examination.

The advantage of the stress-first protocol is that it can be optionally converted to stress-only when the stress MPI is normal, thus avoiding the need for a resting isotope dose and significantly reducing radiation exposure and increasing laboratory throughput (I). Performing stress-only MPI saves 30% to 60% in radiation exposure (M). Recent studies have shown that a normal stress-only MPI study carries the same prognosis for event-free survival as traditional stress-rest or rest-stress protocols. (M6, M7, A31, M10, M11)

The interpretation of MPI involves the visual and semi-quantitative analysis of stress supine and prone perfusion images to determine differences in perfusion, which is subjective and can lead to inter-evaluator variability (J2). Differences in analyses performed by different evaluators can lead to significant differences in...
decision-making; therefore, inter-evaluator agreement plays an important role in the diagnostic performance of a diagnostic test (C6, J4).

In our study, when evaluators were evaluated internally, Cohen’s kappa analysis results indicate that the final decisions for supine1, prone1, supine1+prone1, and supine2, prone2, supine2+prone2 are characterized by low concordance. However, the inter-evaluator final decisions for supine1-supine2 and prone1-prone2 show moderate concordance, while the final decisions for supine1+prone and supine2+prone2 demonstrate strong concordance (kappa: 0.846, p<0.001). Inter-evaluator concordance significantly improves when two-position supine/prone imaging is used, as compared to supine or prone imaging alone.

Inferior wall defects may cause more false positives in the supine study and anteroseptal defects in the prone study. It has been reported that the proximity of the heart to the anterior chest wall in prone imaging and diaphragmatic attenuation in supine imaging probably produce these defects. (O, O5) In our study, consistent with the literature, false positive rates were higher in favor of RCA in supine imaging than in prone imaging, and false positive rates in the LAD area were higher in prone imaging than in supine imaging. False positivity rates in LAD and RCA sites were similar in prone imaging. The false positive rates in the LAD and RCA regions are similar in prone imaging. Furthermore, the evaluation of supine1+prone1 and supine2+prone2 images reveals that the need for rest is significantly attributed to the RCA vessel region for both evaluators. We believe that artifacts are the most important factor that impairs correlation and agreement within and between evaluators.

The attenuation artifact is one of the most common artifacts in MPI and is typically related to the diaphragm affecting the inferior wall in males, as in our study (J).

This study has several limitations. First, it is a retrospective study. Secondly, we did not use CAG as the gold standard. This may seem like a limitation, but in our study, we did not try to detect CAD in these patients, we did not examine the prognosis, and we only tried to determine the need for rest after stress imaging. There should be a strong clinical or MPI suspicion to perform CAG. However, only 11% of our patients underwent CAG after stress + rest imaging. Third, the differences in results between our expert raters, especially for single supine and single prone images, reflect the different reading styles of our expert physicians and show the overall limitation of visual assessment. (J).

**Conclusion:** In men, we observed that supine and prone imaging were not superior to each other in deciding the need for rest. Supine+prone imaging reduced the need for rest by at least 60 percent compared to supine-only or prone-only imaging. While supine imaging alone caused more false positives in the RCA territory, we observed similar false positive results with prone imaging in the LAD and RCA territories. Supine+prone imaging may be preferred over supine-only and prone-only imaging due to reduced cost, time, and radiation exposure for patients.

**References**


**Figure 1.** Combined stress supine-prone myocardial perfusion imaging

A 51-year-old obese male patient initially underwent stress supine imaging, which showed marked hypoperfu-
sion in the inferior wall (RCA territory) (a). Stress prone imaging was then performed to investigate whether this appearance was due to soft tissue attenuation and activity uptake in this area was within physiologic limits (b). After combined stress supine-prone imaging, this area was considered to be a soft tissue artifact, thus eliminating the need for rest imaging after stress imaging.

Figure 2. Image evaluation algorithm

Supine Imaging Evaluation Prone Imaging Evaluation

Decision: No need for rest imaging

Decision: No need for rest imaging

Desicion: Supine+Prone Imaging Evaluation

Decision: No need for rest imaging Desicion: Rest imaging is required.

Table 1. The evaluators’ results of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy in determining the need for rest work.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity(%)</th>
<th>Specificity (%)</th>
<th>PPV(%)</th>
<th>NPV(%)</th>
<th>Accuracy(%)</th>
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<tbody>
<tr>
<td>Supine1</td>
<td>100</td>
<td>66.5</td>
<td>34.8</td>
<td>100</td>
<td>71.6</td>
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<tr>
<td>Prone1</td>
<td>100</td>
<td>70.6</td>
<td>39.2</td>
<td>100</td>
<td>75.3</td>
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<tr>
<td>Supine2</td>
<td>100</td>
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<td>32.9</td>
<td>100</td>
<td>76.2</td>
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<tr>
<td>Prone2</td>
<td>100</td>
<td>70.2</td>
<td>37.1</td>
<td>100</td>
<td>74.7</td>
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Table 2. Vascular territory where the need for rest originates

<table>
<thead>
<tr>
<th></th>
<th>LAD n (%)</th>
<th>RCA n (%)</th>
<th>Cx n (%)</th>
<th>LAD+RCA n (%)</th>
<th>Total n</th>
</tr>
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<tbody>
<tr>
<td>Supine1</td>
<td>31 (13.5)</td>
<td>193 (83.9)</td>
<td>2 (1)</td>
<td>4 (2)</td>
<td>230</td>
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<tr>
<td>Prone1</td>
<td>69 (33.8)</td>
<td>128 (62.7)</td>
<td>1</td>
<td>6 (3)</td>
<td>204</td>
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<tr>
<td>Supine1+prone1</td>
<td>12 (15)</td>
<td>66 (82.5)</td>
<td>1</td>
<td>1</td>
<td>80</td>
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<tr>
<td>Supine2</td>
<td>32 (16.6)</td>
<td>154 (79.8)</td>
<td>3</td>
<td>4</td>
<td>193</td>
</tr>
<tr>
<td>Prone2</td>
<td>69 (34.3)</td>
<td>125 (62.5)</td>
<td>2</td>
<td>5</td>
<td>202</td>
</tr>
<tr>
<td>Supine2+prone2</td>
<td>11 (14.9)</td>
<td>60 (81.1)</td>
<td>1 (1.4)</td>
<td>2 (2.7)</td>
<td>75</td>
</tr>
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Table 3. False positive rates of evaluators in the whole group and by vessel site.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Supine1</th>
<th>Prone1</th>
<th>Supine2</th>
<th>Prone2</th>
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<tr>
<td>Whole grup</td>
<td>33.4</td>
<td>29.4</td>
<td>28</td>
<td>29.7</td>
</tr>
<tr>
<td>LAD zone</td>
<td>11.2</td>
<td>35.4</td>
<td>14</td>
<td>30.7</td>
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<tr>
<td>RCA zone</td>
<td>46.4</td>
<td>31</td>
<td>45</td>
<td>35</td>
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Table 4. Cohen’s kappa agreement analysis results within each evaluator and between evaluators
INTRA-EVALUATOR AGREEMENT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>kappa</th>
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<tr>
<td>Supine1 - prone1</td>
<td>0.322</td>
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<td>Supine1 - supine1+prone1</td>
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<td>Prone1 - supine1+prone1</td>
<td>0.373</td>
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<tr>
<td>Supine2 - prone2</td>
<td>0.278</td>
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<tr>
<td>Supine2 - supine2+prone2</td>
<td>0.384</td>
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<tr>
<td>Prone2 - supine2+prone2</td>
<td>0.353</td>
<td>&lt;0.001</td>
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</table>

INTER-EVALUATOR AGREEMENT

<table>
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<tr>
<th>Parameter</th>
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<th>p</th>
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<tbody>
<tr>
<td>Supine1 - supine2</td>
<td>0.623</td>
<td>&lt;0.001</td>
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<tr>
<td>Prone1 - prone2</td>
<td>0.635</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supine1+prone1 - supine2+prone2</td>
<td>0.846</td>
<td>&lt;0.001</td>
</tr>
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Figure Legends

Figure 1. Combined stress supine-prone myocardial perfusion imaging
A 51-year-old obese male patient initially underwent stress supine imaging, which showed marked hypoperfusion in the inferior wall (RCA territory) (a). Stress prone imaging was then performed to investigate whether this appearance was due to soft tissue attenuation and activity uptake in this area was within physiologic limits (b). After combined stress supine-prone imaging, this area was considered to be a soft tissue artifact, thus eliminating the need for rest imaging after stress imaging.

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