

## Myocardial perfusion imaging in patients with a recent, normal exercise test

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### Abstract

**AIM:** To investigate the added value of myocardial perfusion scintigraphy imaging (MPI) in consecutive patients with suspected coronary artery disease (CAD) and a recent, normal exercise electrocardiography (ECG).

**METHODS:** This study was a retrospective analysis of consecutive patients referred for MPI during a 2-year period from 2006-2007 at one clinic. All eligible patients were suspected of suffering from CAD, and had performed a satisfactory bicycle exercise test (*i.e.*, peak heart rate > 85% of the expected, age-predicted maximum) within 6 mo of referral, their exercise ECG was had no signs of ischemia, there was no exercise-limiting angina, and no cardiac events occurred between the exercise test and referral. The patients subsequently underwent a standard 2-d, stress-rest exercise MPI. Ischemia was defined based on visual scoring supported by quantitative segmental analysis (*i.e.*, sum of stress score > 3). The results of cardiac catheterization

were analyzed, and clinical follow up was performed by review of electronic medical files.

**RESULTS:** A total of 56 patients fulfilled the eligibility criteria. Most patients had a low or intermediate ATP III pre-test risk of CAD (6 patients had a high pre-test risk). The referral exercise test showed a mean Duke score of 5 (range: 2 to 11), which translated to a low post-exercise risk in 66% and intermediate risk in 34%. A total of seven patients were reported with ischemia by MPI. Three of these patients had high ATP III pre-test risk scores. Six of these seven patients underwent cardiac catheterization, which showed significant stenosis in one patient with a high pre-test risk of CAD, and indeterminate lesions in three patients (two of whom had high pre-test risk scores). With MPI as a gate keeper for catheterization, no significant, epicardial stenosis was observed in any of the 50 patients (0%, 95% confidence interval 0.0 to 7.1) with low to intermediate pre-test risk of CAD and a negative exercise test. No cardiac events occurred in any patients within a median follow up period of > 1200 d.

**CONCLUSION:** The added diagnostic value of MPI in patients with low or intermediate risk of CAD and a recent, normal exercise test is marginal.

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**Key words:** Single photon emission tomography; Ischemic heart disease; Myocardial perfusion imaging; Pre-test risk; Post-test risk; Added value; Exercise electrocardiography

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## INTRODUCTION

Treadmill or bicycle exercise electrocardiography (ECG) has been the test of choice for many years for the diagnosis of coronary artery disease (CAD) for reasons of diagnostic performance, cost, and availability. According to the American guidelines, exercise testing remains the test of choice among symptomatic patients with low or intermediate pre-test risk of CAD, provided the patient is able to exercise and the ECG is analyzable for ischemia<sup>[1]</sup>. A normal exercise test is consistent with a good prognosis with regard to cardiac events and cardiovascular and overall mortality<sup>[2]</sup>.

In patients with intermediate or high pre-test risk of CAD, non-invasive imaging methods and invasive coronary catheterization are preferred<sup>[3-6]</sup>. Myocardial perfusion scintigraphy imaging (MPI) is one of the most frequently used non-invasive methods for the assessment of the extent and severity of ischemia in patients with intermediate risk of CAD<sup>[6]</sup>. Several studies have shown that exercise or pharmacological MPI is superior to exercise ECG for the identification of ischemic heart disease in these patients<sup>[7-9]</sup>. Still, the use of MPI is considered inappropriate in patients with a low risk of CAD and the ability to exercise with an analyzable ECG<sup>[1]</sup>. Thus, the diagnostic performance of MPI in low-risk patients and its added value to a normal exercise ECG remain unclear. There are contradictory recommendations in the international guidelines on the management of patients with a normal exercise test but continued suspicion of CAD<sup>[1,10]</sup>. Apparently, no trials have directly addressed this issue. The purpose of this study was to evaluate the diagnostic outcome of MPI in patients with a recent history of a normal bicycle exercise ECG.

## MATERIALS AND METHODS

### Patients

Retrospective data were extracted from consecutive patients who performed a bicycle exercise MPI from January 1, 2006 through December 31, 2007 in a single nuclear medicine center at a regional hospital. The inclusion criteria included the following: (1) the patient was referred for MPI due to suspicion of CAD; (2) the patient had performed a bicycle exercise ECG within six months of referral; (3) the symptoms were unchanged from the time of the exercise ECG to MPI, and no cardiovascular events had occurred; (4) the maximum heart rate obtained at the referral exercise ECG test was at least 85% of the expected age-related maximum; (5) the exercise test was not terminated due to exercise-limiting angina; (6) the baseline ECG was suitable for the assessment of exercise-induced ischemia; and (7) the exercise ECG was classified as negative for ischemia according to the European guidelines for exercise ECG<sup>[10]</sup>. Patients with known CAD were excluded. Pre-test risk of CAD was calculated per the ATPIII classification.

### Referral exercise ECG

All original exercise ECGs were evaluated and reported by a trained cardiologist at the time of testing. Additionally, all exercise tests were retrospectively reviewed by another board-certified cardiologist. In the case of discrepancy between the initial reading and the second opinion, a third cardiologist read the test, and a decision was made based on majority voting. The post-test risk of cardiovascular events was calculated with DanStress<sup>®</sup> software (Svendborg, Denmark) using the algorithm provided by Mark *et al*<sup>[2]</sup>.

### Myocardial perfusion scintigraphy

All MPIs were performed as a two-day, stress-rest standard protocol with two days between the stress and the rest tests, as previously described<sup>[11]</sup>. No attenuation correction was used. Patients with a normal stress MPI did not have a rest MPI. All MPIs were initially reported as positive or negative for ischemia by subjective analysis only. Therefore, all MPIs were retrospectively reviewed in a blinded fashion by a board-certified nuclear medicine physician without any clinical information. Manual segmental scoring was performed using a 17-segment model with a score from 0 to 4 for each segment, from which the sum of stress score (SSS), the sum of rest score (SRS), and the sum of difference score between stress and rest images (SDS) were calculated<sup>[12]</sup>. In addition, SSS, SRS and SDS were automatically calculated with dedicated software. A SSS score of 0 to 3 was considered to be normal, and SSS > 3 to be abnormal<sup>[13]</sup>. In the case of discrepancy in disease classification (*i.e.*, normal or abnormal) between the automatic and manual score, a second nuclear medicine physician performed an additional manual segmental score, and the decision was determined by majority voting. Further in this manuscript, ischemia was present only if confirmed by subjective visual interpretation as well a SSS > 3.

### Coronary catheterization

Cardiac catheterization was performed in accordance with the standard institutional practice and current guidelines<sup>[10]</sup>. A significant stenosis required any luminal narrowing of 70% or more of the diameter of a major epicardial vessel or 50% or more of the diameter of the left main coronary artery. Any investigation with no more than 20% luminal narrowing of any vessels was classified as normal. Results other than stenosis or normal were reported as indeterminate. All findings by angiography were assessed by a board of cardiologists, and the report represented their consensus.

### Clinical follow up

Clinical follow up was performed to assess the cardiovascular event rates in the study population. The institutional electronic patient file system was reviewed for hospital admissions and outpatient contacts for the study population, and any cardiovascular events (cardiac and non-

**Table 1 Patient demographics and clinical variables n (%)**

Men/women (n)	32/24
ATPIII 10-year CAD risk	
Low (< 10%)	33 (59)
Intermediate (10% to 20%)	17 (30)
High (20% and above)	6 (11)
Individual CAD risk factors	
Hypertension	22 (39)
Diabetes	1 (2)
Hypercholesterolemia	21 (38)
Body mass index > 30 kg/m <sup>2</sup>	8 (14)
Family history of CAD	25 (47)
Smoking (current or former)	31 (55)
Current medication	
Beta blockers	3 (5)
ACE inhibitor or Angiotensin II receptor antagonists	4 (7)
Diuretics	4 (7)
Calcium channel blockers	5 (9)
Aspirin	33 (59)
Clodipogrel	1 (2)
Statins	10 (18)
Slow release nitrates	1 (2)
Prior non cardiac vascular conditions	
Stroke or TIA	2 (4)
PAD	0 (0)

CAD: Coronary artery disease; PAD: Peripheral arterial occlusive disease; TIA: Transient ischemic attack.

cardiac) were recorded.

### Ethical approval

The study was approved by the Danish Data Protection Agency. Retrospective informed consent to obtain data from patient files was obtained through an approval by the Danish Board of Health. Due to the retrospective design, no approval by an Ethical Committee was required.

### Statistical analysis

Descriptive statistics comprised means and standard deviations of the mean (SD) and proportions (%). Exact confidence limits of proportions were read from Geigy Scientific Tables (volume 2, 1998; CIBA-GEIGY Ltd, Basel, Switzerland). No analytical statistics were used.

## RESULTS

### Patient population

Of 179 patients who underwent exercise MPI during the observation period, 56 patients fulfilled the eligibility criteria. The main reasons for exclusion were no prior exercise test ( $n = 97$ ), known CAD ( $n = 5$ ), and criteria related to the referral exercise test such as ECG compatible with ischemia ( $n = 15$ ), insufficient heart rate response ( $n = 4$ ), and lack of access to the original exercise test data ( $n = 2$ ). The mean time from exercise ECG to MPI was 82 d (range: 8-179 d). Patient demographics and clinical variables are shown in Table 1. A large proportion of patients had hypertension and hypercholesterolemia so mild that it was not considered therapy-requiring by the

referring physicians. A total of 35 patients were asymptomatic at baseline. Functional grading of angina showed Canadian Cardiovascular Society (CCS) grades 1-2 in 11 patients and grades CCS 3-4 in 8 patients; data was missing in two patients. No patients had known heart failure.

### Referral exercise ECG

All patients terminated the exercise test because of exhaustion or muscle fatigue. No patients had exercise-limiting angina. The mean peak heart rate was 164 beats per minute, which corresponded to 102% (range 87% to 128%) of the predicted, age-adjusted peak heart rate. The mean workload was 155 W (96%, range 60% to 160%). Twelve patients (21%) reported non-specific chest pain, and the remainder of the patients (79%) were asymptomatic during the exercise test. The mean post-test Duke score was 5 (range -2 to 11), which translated into a low post-test risk in 37 patients (66%) and a moderate risk in 19 patients (34%).

### MPI

A total of 53 of 56 patients completed the exercise MPI with a heart rate of least 85% of the age-predicted peak heart rate (mean 99.4%). The mean workload was 166 W. One patient was stopped at 84% of the peak heart rate due to exercise-limiting angina (see later). Two patients failed to reach their target heart rate, and they underwent an adenosine stress test with 25 W of bicycle exercise<sup>[11]</sup>. Stress-only MPI was performed in 14 (25%) of the patients. The criteria for accepting a stress-only test were as previously described<sup>[14]</sup>.

A total of 7 patients were reported as suffering from ischemia and presented also with quantitative, documented ischemia (SSS > 3) with reversible defects in most patients (Table 2).

Three patients were reported as normal in the original MPI report (two patients with low risk and one patient with intermediate risk) but showed SSS > 3 by segmental score as performed as part of this retrospective analysis. None of these patients had reversible defects. MPI was performed without attenuation correction, and segmentation may be falsely high. Based on minor fixed perfusion defects, and normal wall motion pattern in the affected regions, such patients are mostly reported as normal. None of these patients underwent catheterization or experienced cardiac events during the follow up period.

### Coronary catheterization

All patients but one in Table 2 with reported ischemia as well as SSS > 3 underwent cardiac catheterization. MPI served as a gatekeeper for catheterization. Thus, the remainder 49 patients with a visual normal MPI (as well as a normal exercise test) were not routinely referred for cardiac catheterization. However, 3 of these 49 patients underwent catheterization during the follow up and none showed significant stenosis.

One patient with a positive MPI and SSS > 3 was diagnosed with significant CAD (patient 4, Table 2). This

**Table 2** Clinical and imaging data for patients classified with coronary artery disease by myocardial perfusion imaging

Patient No	Gender	Age (yr)	ATPⅢ pre test risk	Duke post test risk	SSS > 3	SDS > 3	Cardiac catheterization
1	Male	79	High	Intermediate	+	+	Indeterminate
2	Male	52	Intermediate	Intermediate	+	+	Normal
3	Male	71	Intermediate	Low	+	+	Normal
4	Male	43	High	Intermediate	+	+	Significant stenosis
5	Female	65	Low	Low	+	+	Not done
6	Male	63	Intermediate	Low	+	+	Indeterminate
7	Male	48	High	Low	+	+	Indeterminate

SSS: Sum of stress score; SDS: Sum of difference score.

patient with significant two-vessel stenosis had a high pre-test risk of CAD, completed the referral exercise test with non-specific chest pain, reached 104% of peak heart rate, presented an exercise capacity of 200 W, showed no ECG changes, and had an intermediate Duke post-test risk score. He experienced no cardiac events or aggravation of symptoms from referral exercise test to MPI. During MPI exercise testing 4.5 mo later, he experienced exercise-limiting angina and received the radiotracer at 84% of his predicted peak heart rate. There were no ECG changes; however, the MPI showed significant ischemia.

Among the 50 patients with a low or intermediate pre-test risk of CAD, the final diagnostic work up, with the clinical MPI report as a gatekeeper for cardiac catheterization, showed no significant anatomical stenosis in any of these patients (0/50; 0%, 95%CI: 0.0-7.1). One of these patients had an indeterminate lesion (patient 6 in Table 2).

### Clinical follow-up

The median follow up time was 1277 d (range 917-1566 d). No patients had any documented cardiac events, such as non-fatal myocardial infarction, cardiac interventions (percutaneous coronary interventions or bypass surgery), or sudden cardiac death (0/56; 0% 95%CI: 0.00-6.38). All patients were alive at follow up. One patient experienced a non-fatal stroke (patient 7 in Table 2).

## DISCUSSION

In this study, we investigated the diagnostic value of MPI in patients with a recent, normal exercise ECG. To the best of our knowledge, this study is the first of its kind. Among 56 patients one patient had a significant stenosis as shown by cardiac catheterization. This patient had a high pre-test risk of CAD and should, according to current guideline recommendations, be referred directly for coronary catheterization. By contrast, an exercise MPI did not reveal any significant anatomical stenosis in any of 50 patients with low to intermediate pre-test risk of CAD and a recent, normal exercise ECG test. The majority of these patients had a negative MPI (and thus no subsequent catheterization) or a positive MPI with either normal vessels or insignificant anatomical stenosis).

MPI has solid documentation for the diagnosis

and risk stratification of patients with CAD<sup>[6]</sup>. Several groups have documented that the imaging results from MPI have higher sensitivity and specificity compared to exercise data obtained from the same exercise MPI<sup>[7-9]</sup>. However, results from a recent, large study showed that the perfusion imaging component of an exercise MPI did not add diagnostic value in patients who were able to perform an adequate workload<sup>[15]</sup>. Most studies with exercise MPI include patients with intermediate risk of CAD, *i.e.*, the target population for MPI. The difference in diagnostic performance between exercise ECG and MPI in low-risk patients with a low prevalence of CAD remains unknown. Despite guideline recommendations against the use of MPI in low-risk patients, MPI is used widely for such patients<sup>[1,16]</sup>. The European Society of Cardiology (ESC) gives a class I recommendation for MPI in patients with an inconclusive exercise ECG but reasonable exercise tolerance and a low to intermediate risk of CAD in whom the diagnosis is still in doubt<sup>[10]</sup>. The clinical documentation for this recommendation is mainly based on patients with established CAD, including patients with prior coronary artery bypass grafting<sup>[17]</sup>. The ESC guidelines also give a class I recommendation for exercise ECG in patients with intermediate risk of CAD and a class II b recommendation for low-risk patients<sup>[10]</sup>, which is in direct contrast to US guidelines, which recommend exercise ECG for low-risk patients and MPI for intermediate risk patients<sup>[1]</sup>. The discrepancy in recommendations across guidelines has been the subject of several recent systematic reviews<sup>[18,19]</sup>. There is a need for evidence-based guidelines for cardiovascular imaging<sup>[20]</sup>.

In patients with low or intermediate risk of CAD and the ability to exercise, exercise ECG may still provide a sufficient diagnostic test and be a valid gate-keeper modality for additional anatomical and/or functional investigations. This is in accordance with US guidelines<sup>[1]</sup>. Our findings are also consistent with a recent, large study showing that the perfusion imaging component of an exercise MPI did not add diagnostic value in patients who were able to perform an adequate workload<sup>[15]</sup>.

There are several limitations to this study. First, we recognize that the size of this study population is limited. However, we included well-characterized patients with a technically successful but negative exercise ECG referred for MPI for further diagnostic work up. To the best of our knowledge, no prior studies have described such pa-

tients. Second, cardiac catheterization was not performed in all of the patients, and this may influence the diagnostic accuracy. However, it would not be appropriate to do cardiac catheterization in low-risk patients with a normal exercise and MPI. Even with a positive MPI, catheterization should be optional, depending on the symptoms and extent of functional ischemia. This situation reflects the emerging scenario where only patients with notable ischemia are candidates for revascularization. Recent studies have confirmed clinical benefit to intervention beyond optimal medical therapy in cases of severe ischemia only<sup>[21,22]</sup>. The extent of symptoms and co-morbidities may have influenced the decision among cardiologists not to perform coronary catheterization. Nevertheless, our study has sufficient power with regards to the negative predictive value of a normal exercise test in patients with low or intermediate risk. None of 50 patients with low or intermediate risk by exercise test were found to have significant stenosis with MPI as the gatekeeper for catheterization (one patient had a non-significant stenosis).

In recent years, a number of new non-invasive tests have been introduced for the diagnosis of CAD, with computerized tomography angiography as one of the most promising techniques<sup>[3]</sup>. In centers where non-invasive imaging methods are available, such methods will eventually be used as a first-line option for the non-invasive diagnosis of CAD. In other situations, exercise ECG may persist as a gatekeeper modality for further diagnostic work up. Recent studies have shown that coronary computerized tomography angiography surpasses exercise-ECG in cost only, but not in diagnostic performance<sup>[23]</sup>. Further information is expected from large, ongoing trials comparing different types of anatomical and functional testing methods in patients with low to intermediate risk of CAD.

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## COMMENTS

### Background

Diagnosis of coronary artery disease (CAD) is important to initiate appropriate interventions and to prevent future major cardiovascular events. Depending of the risk of disease, different diagnostic tests are recommended. The choice of test reflects the diagnostic characteristics of the test (e.g., positive and negative predictive diagnostic values and prognostic value), availability, cost, and risk of procedure. Generally, tests at each level serve as a gate keeper for next-level tests.

### Research frontiers

Myocardial perfusion scintigraphy imaging (MPI) is generally indicated for patient with intermediate risk of CAD. International guidelines display diverging recommendations for additional imaging in low risk patients with normal exercise tests.

### Innovations and breakthroughs

Prior studies have examined the importance of exercise data with imaging

results in exercise MPI. The independent values of these data are relevant for intermediate risk patients referred directly for MPI. This is the first study examining directly the added value of MPI in low to intermediate risk patients who recently performed a normal exercise test.

### Applications

By studying the diagnostic value MPI, used as a gate keeper for subsequent cardiac catheterization, for identification of significant stenosis, it was revealed that the diagnostic value of additional imaging was marginal in patients with low and intermediate risk of CAD. The data on high risk patients are not powered to provide firm conclusions.

### Terminology

MPI is a functional test for myocardial ischemia. The relation of functional assessment of ischemia and anatomical stenosis is much debated.

### Peer review

The authors demonstrated that myocardial perfusion imaging following normal exercise electrocardiography (ECG) did not add diagnostic value in patients with a low or intermediate risk of coronary artery disease, if they could be able to perform an adequate work. No significant conclusions could be made in the subgroup of patients with high-risk. These results support the current and logical clinical management in CAD-suspected patients with normal maximal ECG-stress tests. The study results are in line with previous studies.

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