

Evaluation of Patients with Acute Chest Pain Using SPECT Myocardial Perfusion Imaging: Prognostic Implications of Mildly Abnormal Scans

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ABSTRACT: **Background:** While patients presenting to emergency departments (ER) with chest pain are increasingly managed in chest pain units (CPU) that utilize accelerated diagnostic protocols for risk stratification, such as single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), data are lacking regarding the prognostic implications of mildly abnormal scans in this population.

Objectives: To evaluate the prognostic implications of mildly abnormal SPECT MPI results in patients with acute chest pain.

Methods: Of the 3753 chest pain patients admitted to the CPU at the Leviev Heart Center at Sheba Medical Center between 2006 and 2010, 1593 were further evaluated by SPECT MPI. Scans were scored by extent and severity of stress-induced perfusion defects, with 1221 patients classified as normal, 82 with myocardial infarction without ischemia, 236 with mild ischemia, and 54 with more than mild ischemia. Mild ischemia patients were further classified to those who did and did not undergo coronary angiography within 7 days.

Results: Mild ischemia patients who underwent coronary angiography were more likely to be male (92% vs. 81%, $P = 0.01$) and to have left anterior descending ischemia (67% vs. 42%, $P = 0.004$). After 50 months, these patients returned less often to the ER with chest pain (53% vs. 87%, $P < 0.001$) and had a lower combined endpoint of acute coronary syndrome and death (8% vs. 16%, $P < 0.001$).

Conclusions: Compared to patients with chronic stable angina, patients presenting with acute chest pain exhibiting mildly abnormal SPECT MPI findings should perhaps undergo a more aggressive diagnostic and therapeutic approach.

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KEY WORDS: chest pain, myocardial perfusion, ischemia, single-photon emission computed tomography (SPECT), myocardial perfusion imaging (MPI)

the misdiagnosis of acute coronary syndrome (ACS) may have significant consequences. Two-thirds of patients presenting to the ER with chest pain are hospitalized, and of these only 15% are ultimately diagnosed with ACS. Of the remaining third who are discharged from the ER, 5% eventually suffer from ACS [1-3]. In recent years, chest pain units (CPU) have provided thorough and rapid evaluation of patients presenting to the ER with chest pain [4,5] with studies proving their cost effectiveness [6,7]. As a result, the recent American Heart Association/American College of Cardiology guidelines have emphasized the effectiveness of CPU in the evaluation of patients with acute chest pain [8]. Management of patients in CPU involves the use of accelerated diagnostic protocols for risk stratification in which single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) plays a central role. Recent studies [9,10] have shown that in patients with stable coronary artery disease (CAD), the finding of mild ischemia by MPI may warrant conservative management. However, data are lacking regarding the prognostic implications of mildly abnormal scans in patients presenting with chest pain suspicious for ACS, such as those in the CPU population.

The aim of our study was to examine the prognostic significance of mild ischemia detected by MPI in a real-world setting, comprising a large cohort of patients presenting with acute chest pain and undergoing evaluation by a dedicated CPU team using a strict protocol.

PATIENTS AND METHODS

STUDY POPULATION

Between 2006 and 2010, we studied 3753 consecutive patients who presented to the ER with chest pain and were subsequently admitted to the CPU. Inclusion criteria for CPU admission included age > 20 years and chest pain that was considered by the attending physician to be suggestive of cardiac origin requiring hospitalization, to rule out ACS as well as unexplained by local trauma or other proven non-cardiac pathology. Exclusion criteria included: high-risk probability for ACS, baseline electrocardiographic changes suggesting acute ischemia or infarction, increased cardiac troponin during evaluation in

Over the past two decades, major advances have affected the treatment of triage and evaluation of patients presenting with chest pain. Nevertheless, considerable time and effort are still devoted to the diagnosis of patients presenting to the emergency department (ER) with chest pain, especially since

the ER, and conditions requiring intravenous medications or chronic nursing care.

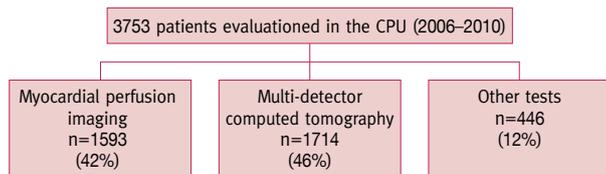
STUDY DESIGN

Hospitalized patients were monitored and observed for a minimum of 12 hours using a computerized ST-segment monitoring system, followed by a repeat electrocardiogram and cardiac troponin measurements. Patients were hospitalized for further evaluation if one of the following was found: new ischemic electrocardiographic changes, increased troponin levels, ST-analyzer changes suggestive of myocardial ischemia, and/or ongoing chest pain assumed to be ischemic by the evaluating cardiologist. Patients free of these findings were referred for multi-detector computed tomography (n=1714), SPECT MPI (n=1593), or other tests (n=446) [Figure 1].

For MPI, multi-stage treadmill exercise testing using the Bruce protocol was performed to enable patients to achieve 85% of maximal predicted heart rate. If patients were unable to exercise or reach 85% of their maximum predicted heart rate, a dipyridamole pharmacologic stress test was performed. After dipyridamole infusion, patients were encouraged to exercise for 3–4 minutes if not contraindicated (complete left bundle branch block, permanent pacemaker). A thallium dose of 104 to 118 MBq was injected intravenously 1 minute before exercise termination, or 4 minutes after termination of dipyridamole infusion. Clinical response was considered positive for ischemia if anginal pain occurred during testing and/or systolic blood pressure decreased by > 0 mmHg during exercise. Positive electrocardiographic response for ischemia was defined as the presence of > 1 mm horizontal or down-sloping or 1.5 mm up-sloping ST-segment depression 8 ms after the J-point during exercise or recovery. Imaging was initiated 8–12 minutes after stress injection of thallium, and repeated at 4 hours thereafter. All studies were subjected to quality control for camera non-uniformity, center of rotation, and patient motion.

Two experienced nuclear cardiologists (RG and AN), blinded to the clinical data, analyzed the myocardial perfusion scintigraphic images. The left ventricle was divided into 17 segments: one for the apical portion (analyzed from the vertical long axis) and 16 for the rest of the myocardium from three representative portions (distal, mid, and proximal) of short-

Figure 1. Patient evaluation flow chart



CPU = chest pain unit

axis tomograms. Segmental thallium-201 uptake was scored by a 4-point scoring system. Patterns of defect reversibility were based on the segmental score change from the initial to the redistribution study as nonreversible, partially reversible, and completely reversible. A pattern of reverse redistribution was defined as nonreversible. Patients were then classified as having normal perfusion, myocardial infarction (MI) without ischemia, mild ischemia (1 or 2 segments in extent, mild in severity), or more than mild ischemia [Figure 2].

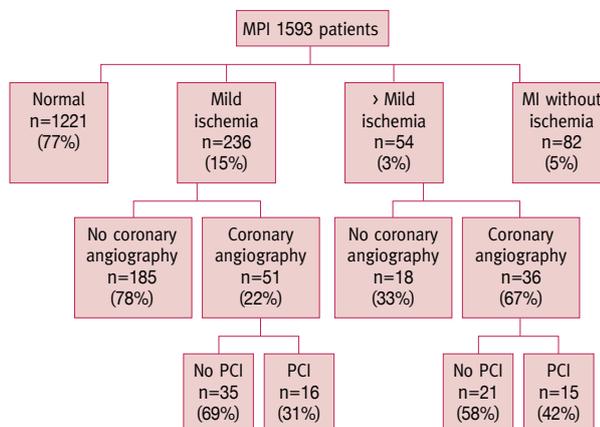
FOLLOW-UP PROCEDURES

Follow-up data were obtained via a telephone interview using a prespecified questionnaire. The prespecified clinical endpoints during follow-up were repeated hospitalizations for chest pain suspected as ACS, ACS (consisting of chest pain in the presence of either electrocardiographic changes suggestive of myocardial ischemia or infarction and/or troponin elevation), coronary angiography, coronary revascularization (either percutaneous or bypass grafting), death, and the combined endpoint of ACS + death. For patients without available follow-up data, we reviewed the medical records and used the national population registry of the Ministry of Interior to evaluate whether the outcome of death had occurred.

STATISTICAL ANALYSES

Statistical analysis was performed using IBM SPSS Statistics version 20 software (IBM Corp, Armonk, New York, USA). Categorical variables were compared using chi-square tests. However, in Table 1, a Student’s independent *t*-test was used for comparison of age (a continuous variable), after normality was confirmed. Moreover, in Table 2, a Z-test was used to compare characteristics (CABG and death) where the percentage was less

Figure 2. Myocardial perfusion imaging findings and subsequent management in the chest pain unit



MI = myocardial infarction; MPI = myocardial perfusion imaging; PCI = percutaneous coronary intervention

Table 1. Characteristics of patients with mild ischemia by myocardial perfusion imaging*

Characteristic	Coronary angiography N=51	No coronary angiography N=185	P value
Age, years	61 ± 10	63 ± 10	0.09
Male	92%	81%	0.01
Hypertension	47%	68%	0.06
Dyslipidemia	78%	84%	0.24
Diabetes mellitus	25%	24%	0.49
Family history CAD	51%	45%	0.29
Smoking	22%	17%	0.30
Prior MI	51%	51%	0.54
Prior PCI	73%	77%	0.33
Prior CABG	16%	16%	0.56
Typical chest pain	12%	9%	0.21
Atypical chest pain	78%	90%	0.07
LAD fixed defect	12%	13%	0.91
CX fixed defect	10%	14%	0.91
RCA fixed defect	8%	9%	0.96
LAD reversible defect	67%	42%	0.004
CX reversible defect	22%	45%	0.04
RCA reversible defect	12%	14%	0.2

*Data are presented as percentages or mean ± SD.

CABG = coronary artery bypass graft surgery, CAD = coronary artery disease, CX = circumflex artery territory, MI = myocardial infarction, LAD = left anterior descending artery territory, PCI = percutaneous coronary intervention, RCA = right coronary artery territory

Table 2. Long-term follow-up of patients with mild ischemia by myocardial perfusion imaging

Characteristic	Coronary angiography N=51	No coronary angiography N=185	P value
Mean follow-up, months	45 ± 17	52 ± 19	
Angiogram	14 (27%)	54 (29%)	0.14
PCI	6 (12%)	28 (15%)	0.26
CABG	0	1 (0.5%)	0.6
Death	0	7 (4%)	0.16
ACS	4 (8%)	22 (12%)	0.29
ACS + death*	4 (8%)	29 (16%)	< 0.001
ER with chest pain	27 (53%)	161 (87%)	< 0.001

*Incidence of combined endpoint (ACS + Death) = 33/230 = 14.3%.

ACS = acute coronary syndrome, CABG = coronary artery bypass graft surgery, ER = emergency department, PCI = percutaneous coronary intervention

than 5%. For all analyses, a statistically significant difference was considered with a *P* value of < 0.05. The study was approved by the Sheba Medical Center institutional review board.

RESULTS

The study comprised 3753 consecutive patients who presented to the ER with acute chest pain and were evaluated in the CPU.

After a clinical evaluation period of at least 12 hours, 1593 patients underwent further evaluation by MPI [Figure 1]. Scans were scored using the extent and severity of stress-induced perfusion defects, and then patients were classified as follows: normal (1221), MI without ischemia (82), mild ischemia (236), and more than mild ischemia (54). Those patients in the mild ischemia group were further classified by whether coronary angiography was performed within 7 days of admission [Figure 2].

As can be seen in Table 1, the results of the patients with mild ischemia who had undergone angiography within 7 days of hospitalization differed from those who did not undergo angiography, regarding two parameters: they were more likely to be male (92% vs. 81%, *P* = 0.01) and to have a greater incidence of LAD ischemia (67% vs. 42%, *P* = 0.004).

We were able to obtain a complete follow-up for 230 (98%) of the 236 patients who had mild ischemia by MPI. The average follow-up period was 50 months (4.2 years). Patient outcome during follow-up is presented in Table 2. We found that the group as a whole had a surprisingly high incidence (14.3%) of the combined endpoint of ACS and death. In the subgroup analysis, those patients who underwent initial angiography were re-admitted less frequently for recurrent chest pain (52.9% vs. 87.0%, *P* < 0.001) than those who did not undergo initial angiography. Of note, the subgroup who initially underwent angiography had a significantly lower combined endpoint of ACS and death (7.8% vs. 15.7%, *P* < 0.001).

DISCUSSION

In 2007, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [9] established that for patients with stable CAD, an initial management strategy of percutaneous coronary intervention plus optimal medical therapy did not reduce long-term death rates, MI, or other cardiovascular events compared with optimal medical therapy alone. Moreover, in the subsequent nuclear sub-study [10], the anti-ischemic benefit of percutaneous revascularization was greatest for patients with moderate to severe ischemia at baseline.

However, patients presenting with acute chest pain suspicious for ACS constitute a different population, and the approach to management in this group is less well-defined. A previous study [11] showed that CPU patients with significant ischemia by MPI benefit from a strategy of early coronary angiography and percutaneous revascularization. However, there is a paucity of data regarding the prognostic implications of mildly abnormal nuclear scans in this population.

In the present study, we examined the long-term prognostic significance of mild ischemia by MPI in a homogeneous patient population presenting with acute chest pain in a real-life setting. During a mean follow-up of about 4 years, we found that this group as a whole had a surprisingly high

incidence (14.3%) of the combined endpoint of ACS and death. Contrary to what may have been erroneously assumed, patients with mild ischemia by MPI do not represent a low-risk population since the presence of mild ischemia, which may not be critical in the immediate term, may nevertheless represent a marker for patients at higher risk. Moreover, those patients with mild ischemia by MPI who underwent coronary angiography returned fewer times to the emergency department with chest pain (53% vs. 87%, $P < 0.001$), and had a lower combined endpoint of ACS and death (8% vs. 16%, $P < 0.001$). These data support the basic hypothesis that in the CPU population coronary angiography should be considered even in patients with only mild ischemia by MPI.

STUDY LIMITATIONS

Since this study reflects a real-life CPU setting, it suffers from all the limitations intrinsic to non-randomized studies, especially the introduction of involuntary bias. However, it should be noted that those patients with mild ischemia who underwent angiography had a greater incidence of LAD ischemia. While it could be assumed that this “sicker” group of patients would have a worse prognosis, in actual fact they had a lower combined endpoint of ACS and death.

CONCLUSIONS

Our results support the notion that the approach to patients with acute chest pain, such as those in the CPU, may need to differ from that in patients with stable CAD. In contrast to patients with chronic stable angina, mildly abnormal MPI findings in CPU patients may have significant prognostic implications, and therefore should perhaps require a more aggressive diagnostic and therapeutic approach.

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Capsule

A subset of platinum-containing chemotherapeutic agents kills cells by inducing ribosome biogenesis stress

Cisplatin and its platinum analogs, carboplatin and oxaliplatin, are some of the most widely used cancer chemotherapeutics. Although cisplatin and carboplatin are used primarily in germ cell, breast and lung malignancies, oxaliplatin is used almost exclusively to treat colorectal and other gastrointestinal cancers. Brumo and colleagues utilized a unique, multi-platform genetic approach to study the mechanism of action of these clinically established platinum anti-cancer agents, as well as more recently developed cisplatin analogs. The authors showed that oxaliplatin, unlike cisplatin and carboplatin, does not kill cells through the DNA-damage response. Rather,

oxaliplatin kills cells by inducing ribosome biogenesis stress. This difference in drug mechanism explains the distinct clinical implementation of oxaliplatin relative to cisplatin, and it might enable mechanistically informed selection of distinct platinum drugs for distinct malignancies. These data highlight the functional diversity of core components of front-line cancer therapy and the potential benefits of applying a mechanism-based rationale to the use of our current arsenal of anti-cancer drugs.

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Eitan Israeli

“A sad soul can kill quicker than a germ”

John Steinbeck (1902–1968), American author of 27 books, winner of the 1962 Nobel Prize in Literature