



Original Article

Attenuated predictive power of a normal myocardial perfusion scan in young smokers ☆☆☆



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ABSTRACT

Background: The negative predictive value of a normal myocardial perfusion image (MPI) for myocardial infarction or cardiac death is very high. However, it is unclear whether a normal MPI, reflecting non-compromised blood flow in the stable state, would have the same prognostic implications in smokers as in patients who do not smoke.

Methods: The incidence of total mortality, cardiovascular mortality, and myocardial infarction was evaluated in 11,812 subjects (14.6% of whom were current smokers at the time of the study) with a normal MPI study and no past history of coronary artery disease during the period 1997 to 2008.

Results: During an average follow-up of 72.4 ± 32.4 months the risk for an acute myocardial infarction in current smokers was approximately 50% higher than the corresponding risk in non-smokers, despite a younger average age. Cox proportional regression models show that current smoking was associated with an increased hazard rate for the composite endpoint below age 60 ($HR = 2.09$, 95%CI 1.43–3.07, $p < 0.001$), but not at older ages ($HR = 1.16$, 95%CI 0.81–1.66, $p = 0.4$).

Conclusions: In individuals below age 60, but not at older ages, current smoking is associated with increased short- and long-term risk of cardiac death and acute myocardial infarction even in subjects with a normal MPI.

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1. Introduction

Coronary atherosclerosis is a chronic disease that begins in childhood and is characterized by the gradual narrowing of the arterial lumen [1]. Once the extent of luminal narrowing reaches a critical degree that compromises coronary blood flow, a condition characterized by stable and reversible myocardial ischemia results [2].

Studies have shown that the sensitivities of exercise, vasodilator myocardial perfusion single photon emission computed tomography (SPECT), and myocardial perfusion imaging (MPI) for the detection of angiographically significant coronary artery disease (CAD) are in the range of 87–89%, while the specificity is around 73–75% [3]. However, retrospective and prospective studies have also shown that the majority of atherosclerotic plaques responsible for future acute coronary events are angiographically mild, and thus not detectable by current imaging

techniques used in clinical practice to detect ischemia [4–6]. Despite these limitations, a large pool of evidence supports the notion that the negative predictive value of a normal MPI for myocardial infarction or cardiac death is over 98% for 3 years, with event rates of approximately 0.45% per year [7].

Tobacco smoking is a major risk factor for cardiovascular disease. For each 10 cigarettes per day there is an incremental increase in cardiovascular mortality in men (18%) and in women (31%) [8]. It has been suggested that smoking exerts its effects by destabilizing existing plaques and/or increasing thrombogenicity, irrespective of plaque size [9–11]. Smoking has been shown to adversely affect endothelial function and inflammation, which can directly contribute to plaque rupture [12,13]. Smoking has also been shown to produce a high oxidative stress burden on the arterial wall, which might cause erosion of the endothelium and render it to a pro-thrombotic state with occlusive thrombus formation, even in the presence of a normal MPI [14]. It is thus unclear whether a normal MPI, reflecting non-compromised blood flow in the stable state, would have the same prognostic implications for future cardiovascular events in smokers as in patients who do not smoke.

The purpose of this study was to compare the clinical cardiovascular outcomes in smokers and non-smokers with no previous coronary artery disease and normal MPI.

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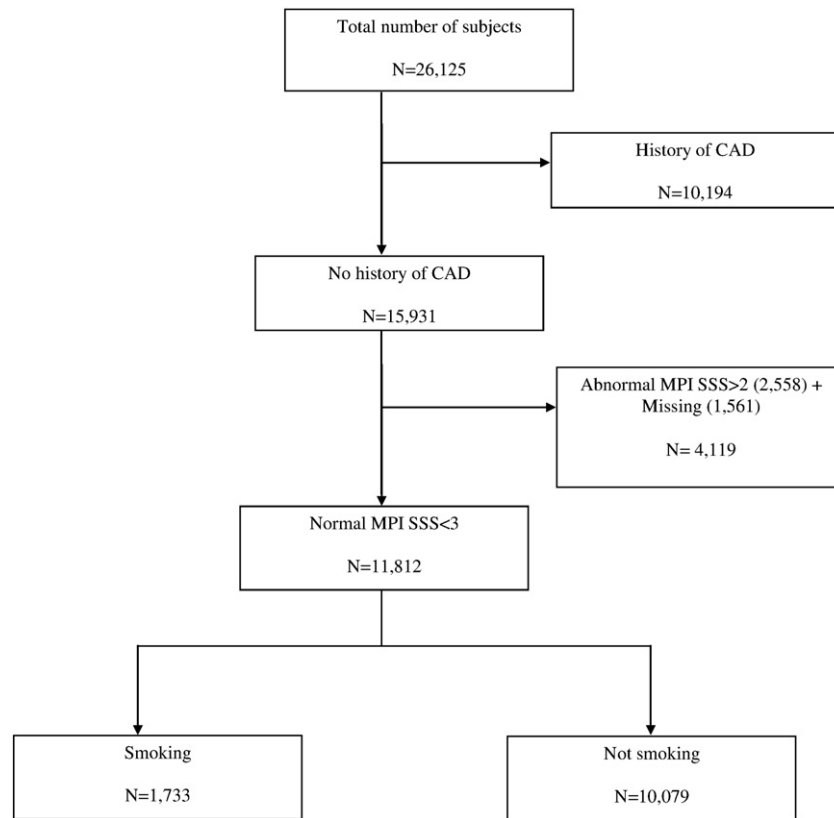


Fig. 1. Flowchart of patient population.

2. Methods

2.1. Patient population

All subjects underwent SPECT MPI at the Soroka University Medical Center (SUMC), an 1100-bed tertiary hospital which is the only provider of acute cardiac care for the population in the Negev district of Israel (610,000 persons) and chronic cardiac care to about 80% of the Negev population who are members of Clalit Health Services (CHS), Israel's largest health service organization. Using the three computerized databases (Cardiology Department, SUMC, and CHS databases) we were able to identify all patients who underwent SPECT MPI studies between 1997 and 2008 and to extract the following information: demographic data, medical history and cardiac risk factors, detailed MPI study data, cardiac events, and mortality data.

All patients who underwent a normal SPECT MPI study and had adequate images, no previous documentation of CAD, and a complete unified database were included in the study. Patients could have been diagnosed with ischemic heart disease after the MPI date and subsequently die due to cardiac causes. Current smoking was defined as patient's self-reported history of smoking and/or computerized diagnosis of smoking at the time of the MPI study. Systemic arterial hypertension (HTN) was defined as a documented history at the time of the MPI study of high blood pressure and/or use of blood pressure lowering medications. Family history of coronary artery disease (CAD) was defined as a CAD event occurring in a first degree relative (men age 55 years or less and women age 65 years or less). Dyslipidemia was defined as a documented diagnosis of dyslipidemia in the patient's file and/or use of a lipid-lowering medication. An established diagnosis of diabetes mellitus and/or insulin or oral hypoglycemic agent treatment defined the presence of diabetes. Obesity was defined as a body mass index (BMI) above 30 kg/m². Since referral to or the result of the MPI study may propagate investigation of risk factors, the first indication

in the computerized database of hypertension, diabetes mellitus, or dyslipidemia within six months following the MPI study was also considered as positive. History of coronary artery disease was defined as a previous myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery, or documented coronary artery disease by coronary angiography prior to the index MPI date.

2.2. Single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) protocol and analysis

Standard protocols were used to trigger ischemia with either treadmill testing or pharmacologic stress testing using intravenous administration of dipyridamole or dobutamine [13]. The radioisotope was injected during the last 60 to 90 s of exercise, or 3 to 4 min after termination of dipyridamole infusion. Thallium 201 (Tl-201) SPECT was performed using a 1-day protocol. Two and a half to 3.5 mCi Tl-201 were injected during the stress portion of the test. Five to 10 min later, tomographic imaging over a 180° arc using the “step-and-shoot” method was performed. Delayed images were acquired 3 to 4 h later. Patients were

Table 1
Baseline characteristics.

Variable	Smokers N = 1733	Non-smokers N = 10,079	p value
Age, years (±SD)	55.3 ± 11.6	62.1 ± 12.4	<0.001
Gender, male (%)	1097 (63.3)	3831 (38.0)	<0.001
Diabetes (%)	513 (29.6)	3466 (34.4)	<0.001
Hypertension (%)	730 (42.1)	5655 (56.1)	<0.001
Family history of CAD (%)	329 (19.0)	1046 (10.4)	<0.001
Dyslipidemia (%)	1410 (81.4)	5116 (50.8)	<0.001
Obesity (%)	851 (49.10)	4618 (45.81)	0.01

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