STATE-OF-THE-ART PAPER

The Effects of Medications on Myocardial Perfusion

Gilbert J. Zoghbi, MD, FACC, Todd A. Dorfman, MD, Ami E. Iskandrian, MD, MACC

Birmingham, Alabama

Antianginal and lipid-lowering medications may modify the results of stress myocardial perfusion imaging. Several studies have shown the beneficial potential of these agents in suppressing myocardial ischemia in patients with known coronary artery disease. The effects of nitrates, calcium-channel blockers, beta-blockers, and statins on myocardial perfusion imaging are likely attributable to changes in myocardial blood flow and myocardial oxygen supply–demand ratio. This comprehensive review examines relevant experimental and clinical published data. Technical issues in image interpretation specific to myocardial perfusion imaging and implications of use of cardiac medications to results of myocardial perfusion imaging are discussed. (J Am Coll Cardiol 2008;52: 401–16) © 2008 by the American College of Cardiology Foundation

Stress myocardial perfusion imaging (MPI) is widely used for the diagnosis and risk assessment of patients with known or suspected coronary artery disease (CAD) (1). Also, MPI lends itself to monitoring the effects of therapeutic interventions such as anti-ischemic medications, gene therapy, and various percutaneous and surgical revascularization modalities.

This review focuses on the effects of medications on stress MPI. Anti-ischemia medications may decrease the size of the perfusion defects, cause false-negative results, and decrease the diagnostic accuracy of the test. On the other hand, improvement in perfusion pattern has been associated with a decrease in the risk of cardiac death or myocardial infarction, especially in patients with a severely abnormal baseline study (2).

Lipid-lowering and antianginal medications, such as calcium-channel blockers (CCBs), beta-blockers (BBs), and nitrates, have been shown to improve the perfusion pattern (Tables 1 to 3). The studies in support of this statement are of 2 types: 1) parallel studies of patients on therapy compared with patients not on such therapy; and 2) serial studies of patients before and after treatment. The first type of studies suffers from important differences in patients' characteristics in the 2 groups, is not helpful in elucidating the true effects, and will only be cited briefly if deemed necessary.

The effects of commonly used medications in patients with CAD on MPI may be secondary to their effects on myocardial blood flow (MBF), tracer kinetics, or myocardial oxygen demand (3–5). In addition, a host of technical variables related to image acquisition and interpretation may be important (3–5). There are no data to indicate that nitrates, CCBs, BBs, and statins affect tracer kinetics apart from their indirect effect on MBF (3–5). It is conceivable that the size and severity of perfusion defects is modified because of changes in the degree of partial volume effect in the presence of regional wall motion abnormalities, for example, myocardial stunning or hibernation and subsequent amelioration of ischemia. Clearly more data are needed. The results of studies that evaluated the effects of antianginal medications and statins on stress MPI in humans are summarized in Tables 1 to 3. The results of experimental studies are summarized in Table 4. Before we discuss the effects of medications, we need to address the technical issues related to imaging.

Technical Issues in Image Interpretation Specific to MPI

Comparing 2 sets of images in the same patient by visual analysis or by using automated programs is more difficult than realized, and the reasons have recently been summarized (Table 5) (6). Absolute quantification (ml/g/min) allows a more precise assessment of serial changes, but such analysis is not yet possible by MPI, and it may be that the detection of small changes is difficult even with the more absolute quantitative methods because of considerable interpatient variability. Knowing the inherent variability of single-photon emission computed tomography (SPECT) imaging is critical to determine whether observed changes in scan interpretation can be ascribed to actual changes due to treatment, changes in the patients' condition, or procedure variability (6). There are few previous studies evaluating agreement rates for sequential imaging. These studies were single center and included small numbers of patients.

**Abbreviations
and Acronyms**

BB = beta-blocker

CAD = coronary artery
disease

CCB = calcium-channel
blocker

CFR = coronary flow
reserve ratio

LDL = low-density
lipoprotein

MBF = myocardial blood
flow

MPI = myocardial perfusion
imaging

PCI = percutaneous
coronary intervention

PET = positron emission
tomography

SPECT = single-photon
emission computed
tomography

The majority of such studies compared inter-reader interpretation of a single image and not 2 sequential images; agreement rates for comparison of sequential images may be lower because acquisition of a second image introduces biological changes, medication effect, and technical variability in acquisition, processing, and interpretation of the images. The analysis often used sample-weighted averages to calculate agreement rates, which gives the category with the highest number of patients the greatest contribution to the average. Finally, agreement rates are usually reported for the overall impression of the scan as normal versus abnormal or normal versus ischemia versus infarct; it is well known that agreement rates are better when categories are narrow rather than wide, such as extent and severity of ischemia (7,8).

Nitrates

Experimental studies. All forms of nitroglycerin preparations release nitric oxide in vascular smooth muscle cells (9). Nitric oxide activates soluble guanylyl cyclase, leading to the production of guanosine 3,5-cyclic monophosphate (cGMP) that facilitates smooth muscle cell relaxation through the dephosphorylation of myosin light chains. This inhibits the interaction between myosin and actin and prevents smooth muscle contraction (10). Nitroglycerin causes marked relaxation of all components of the vascular system and dramatically decreases pulmonary vascular pressure, intraventricular pressure, chamber size, and cardiac output (10). Nitroglycerin therefore may improve myocardial perfusion via a reduction in wall tension (Laplace relation) and myocardial oxygen demand (10–12).

Nitroglycerin decreases coronary vascular resistance and increases the diameter of large conduit vessels (>100 μm); the degree of smaller vessel dilation exceeds that of larger vessels only after the highest doses of nitroglycerin (13). However, total coronary flow does not increase in the presence of obstructive CAD (10,13–17). Nitroglycerin selectively dilates microvessels distal to coronary stenosis, but myocardial perfusion remains constant (17). The anti-ischemic effect of nitroglycerin might also be attributable to the redistribution of coronary flow from normal to ischemic myocardium through dilation of collateral vessels (10,11,18).

Nitroglycerin may also preserve myocardial perfusion through the inhibition of platelet thrombus formation (19–22). Nitric oxide is capable of activating soluble guanylyl cyclase in platelets. This stimulates cGMP production and inhibits thrombin-induced platelet aggregation to adenosine diphosphate by approximately 80% (21), and it decreases platelet aggregation to thrombin (22). Nitric oxide also up-regulates endothelial cell cyclo-oxygenase activity, resulting in a marked increase in the release of the stable metabolite of prostaglandin I2, 6-keto prostaglandin F1alpha, and this metabolite enhances the antithrombotic effects of nitrates by approximately 10-fold (21). Continuous nitroglycerin infusion markedly decreases platelet thrombus formation without affecting coronary flow (19). The antiplatelet effects are subject to tolerance (23).

Clinical studies. The effects of nitrates on MPI were studied with different nitroglycerine doses and modes of administration (Table 1). Earlier studies used exercise planar imaging (21), but later studies used SPECT (24,25). The study designs varied from comparison of studies before and after treatment (24,26,27), a crossover study (28), and randomized, double-blind, placebo-controlled studies (25,29).

The acute administration of sublingual (24) or short-acting nitrates (25) significantly decreased the ischemic perfusion severity or size in the culprit zone compared with placebo (25) or with a baseline study without nitrates (24). Similarly, the chronic administration of long-acting nitrates decreased ischemia severity (27) and perfusion defect size (26,29) compared with placebo (29) or with a baseline study without nitrates (26,27). The improvement in perfusion was greater in patients with large baseline defects than in those with small defects and was independent of changes in heart rate or blood pressure, suggesting that the improvement was mostly attributable to enhancement of MBF (29). In a small study of 15 patients, treatment with nitroglycerin patches for 4 weeks decreased the extent of ST-segment depression but did not influence the perfusion defect severity (28).

In summary, acute or chronic administration of nitrates has been shown to decrease the size and severity of exercise-induced myocardial perfusion defects.

Effects of nitrates on myocardial viability. Nitrates have been used in rest studies to enhance the ability of MPI to detect viable myocardium because they decrease myocardial oxygen demand and improve flow to ischemic areas (by directly dilating stenosed coronary arteries feeding the ischemic myocardium or by redistributing collateral flow to the ischemic myocardium) (24,30). In positron emission tomography (PET) studies, pre-treatment with nitrates increased tracer uptake in the ischemic myocardium compared with that in the nonviable myocardium, resulting in improved viability detection (31,32). Pre-treatment with nitrates improved detection of viable myocardium and predicted post-revascularization recovery in different studies that used resting MPI with the technetium-labeled tracers (tetrofosmin, sestamibi) and with thallium-201 (33–40). In patients with ischemic cardiomyopathy, the prognostic value of SPECT MPI after nitrate was comparable to that of PET imaging (40).

Table 1   **Summary of Studies That Evaluated the Effects of Antianginal Medications on MPI**

Author, Year (Ref. #)	Patients	Treatment	Testing	Perfusion
Nitrates				Perfusion defect score
Eldridge et al., 1987 (28)	15 patients with stable angina and CAD on angiography or abnormal stress MPI Exercise thallium SPECT	NTG patches (16 cm/day) or nifedipine (70 mg/day) for 4 weeks Antianginal medication withheld before test Crossover study	NTG patch − NTG patch +	No difference with and without NTG
Aoki et al., 1991 (24)	7 patients with total or subtotal proximal LAD occlusion and well-developed collaterals Exercise thallium SPECT	0.3 mg sublingual NTG a few minutes before test	NTG − NTG +	Total defect size 23 ± 17% 7 ± 9% (p < 0.05)
Mahmarian et al., 1994 (29)	40 patients with stable angiographic CAD and no prior MI perfusion defects involving ≥5% of the left ventricle Exercise thallium SPECT	Intermittent (12 h on/off) NTG patch (0.4 mg/h) placebo Most patients weaned off antianginal medication before test Randomized, double-blind, parallel, placebo-controlled	Placebo: baseline and at 6.1 ± 1.8 days Patch: baseline and at 6.1 ± 1.8 days	Ischemic defect size 12.3 ± 10.0% to 11.3 ± 12.2% 18.6 ± 10.1% to 10.1 ± 10.5%, p = 0.04
Goller et al., 1995 (25)	30 patients with stable angina and >70% stenosis Exercise Tc-99m SPECT	60 mg sustained release isosobide-5-nitrate administered 5 h before testing Antianginal medication withheld for 2 to 3 days before test Randomized, double-blind, placebo-controlled study	Placebo (baseline treatment) Nitrates (baseline treatment)	Ischemic defect size 35.2 ± 27.6% to 36.6 ± 27.4% (p = NS) 38.2 ± 31.0% to 29.1 ± 33.8% (p < 0.05)
Lewin et al., 2000 (26)	40 patients with chronic stable angina and >10% reversible defect of any coronary vascular territory at baseline Exercise dual-isotope SPECT	Isosorbide mononitrate 60 mg daily for 4 days and 120 mg daily for 35 to 42 days Off antianginal medications for 24 h before test (except isosorbide mononitrate for second and third tests)	Baseline 5 days 35 to 42 days	Total perfusion defect size/SSS 34.9 ± 12.2%/20 ± 10 —/18 ± 10 30.1 ± 12.7%/17 ± 10 (p < 0.002)

BBs

Experimental studies. The major anti-ischemic effect of BBs is a reduction in myocardial oxygen consumption both at rest and during stress (12,41,42). Beta-blockers decrease myocardial oxygen demand through a reduction in heart rate, blood pressure, and myocardial contractility. They also prolong diastole, therefore increasing coronary perfusion time (10,41).

Beta-blockers improve ischemic wall function and preserve regional blood flow, but the benefit of BBs was negated when heart rate reduction was eliminated (41). However, BBs significantly increase myocardial oxygen extraction and markedly decrease myocardial oxygen consumption in ischemic regions by improving microregional distribution of blood flow within the ischemic zone (43). Beta-blockers increase the endocardial-to-epicardial flow ratio, MBF/beat, and relative MBF in ischemic areas (43,44).

Alteration in cardiomyocyte metabolism provides an additional cardiovascular protection against ischemia (45). In a model of coronary occlusion, metoprolol significantly reduced infarct size and markedly increased coronary collat-

eral flow compared with placebo (45). Metoprolol, unlike placebo, reduced myocardial oxygen consumption and maintained myocardial uptake of lactate and nonesterified fatty acids (45). Beta-blockers also protect against ischemia and reperfusion by other mechanisms such as preserving membrane phospholipids, decreasing apoptosis, preserving electrical potential, and enhancing mitochondrial function (46–49).

Clinical studies. Nonrandomized studies compared the exercise MPI results of patients on with those not on BB therapies. However, these studies were in different groups of patients and overall showed a decrease in the sensitivity in detecting CAD in patients on BBs (50,51).

Different doses, types, and modes of administration were used to study the effects of BBs on exercise or dobutamine MPI in the same patients while on or off BBs or in a cross-over study design or a randomized, double-blind, placebo-controlled study design (Table 1).

The chronic administration of oral propranolol in patients undergoing exercise planar MPI improved tracer activity compared with placebo or with baseline studies

| Table 1 | Continued |

Author, Year (Ref. #)	Patients	Treatment	Testing	Perfusion
Beta-blockers				Defect mass: exercise and redistribution
Narahara et al., 1989 (54)	12 patients with chronic stable angina and CAD Exercise thallium SPECT	Randomization to propranolol 40 mg 4 times daily or betaxolol 20 mg/day for 2 weeks Placebo for 5 weeks Beta-blockers were held for 48 h and calcium-channel blockers for 24 h before each test Randomized, placebo-controlled	Placebo Beta-blocker	47 ± 36.3 g and 28 ± 29.8 g 32 ± 27.1 g and 15 ± 23.3 g (p < 0.01 for both defects)
Bridges et al., 1992 (56)	12 patients with CAD on angiography Dipyridamole thallium SPECT	Atenolol 50 mg/day for 1 week Placebo for 1 week Randomized, double-blind and crossover study	Atenolol vs. baseline Placebo vs. baseline	Defect size No difference No difference
Shehata et al., 1997 (55)	17 patients with ischemia on prior MPI Dobutamine Tc-99m SPECT	Intravenous propranolol to a cumulative dose of 8 mg or to a maximum baseline heart rate reduction of 25% Beta-blockers and calcium-channel blockers held 48 and 24 h before test, respectively	Propranolol + Propranolol −	SSS and SDS 14 ± 9 and 7 ± 6 (p = 0.02 for SSS) 18 ± 10 and 10 ± 7 (p = 0.047 for SDS)
Bottcher et al., 1997 (58)	10 healthy volunteers Dipyridamole NH3-PET	Metoprolol 50 mg orally 12 and 1 h before the study	Metoprolol − Metoprolol +	CFR 3.14 ± 0.80 4.61 ± 0.68 (p < 0.01)
Taillefer et al., 2003 (57)	21 patients with catheterization-proven stable CAD Dipyridamole Tc-99m SPECT	Acute administration of placebo, low-dose (up to 10 mg) and high-dose (up to 20 mg) intravenous metoprolol Beta-blockers and calcium-blockers held 48 and 24 h before test, respectively Prospective, randomized, double-blind, placebo-controlled	Placebo Low-dose metoprolol High-dose metoprolol	SSS and SDS 12.0 ± 10.1 and 8.4 ± 8.8 8.7 ± 9.0 and 5.0 ± 6.7 (p < 0.05) vs. placebo 9.3 ± 10.6 and 5.4 ± 7.9 (p < 0.05) vs. placebo
Bottcher et al., 2003 (60)	14 patients with angiography-proven CAD (>70% stenosis) Dipyridamole NH3-PET	Metoprolol 50 mg/day Off antianginal medications (>5 half lives) Randomized	Metoprolol − Metoprolol +	CFR 2.16 ± 0.56 1.87 ± 0.55 (p = NS)
Koepfli et al., 2004 (42)	36 patients with angiographically-documented CAD and stable angina Adenosine NH3-PET	12 weeks treatment with beta-blockers (100 mg metoprolol/day or 50 mg carvedilol/day) Antianginal medication held for 1 week before test Double-blind design	Beta-blocker − Beta-blocker +	CFR in stenotic and remote segments 2.23 ± 0.88 and 2.39 ± 0.83 2.62 ± 1.10 and 2.64 ± 0.75 (p < 0.05 for stenotic and p = NS for remote segments)
Calcium-channel blockers				Perfusion defect score
Eldridge et al., 1987 (28)	15 patients with stable angina and CAD on angiography or abnormal stress MPI Exercise thallium SPECT	NTG patches (16 cm/day) or nifedipine (70 mg/day) for 4 weeks Crossover study	Nifedipine − Nifedipine +	49 ± 28 28 ± 26 (p < 0.01)
Yamazaki et al., 1993 (69)	12 patients with prior MI and 9 patients with angina pectoris Exercise thallium SPECT	Nicorandil 15 mg/day for at least 3 weeks	Nicorandil − Nicorandil +	Percent thallium uptake: MI and angina 52.4% and 56.9% 60.4% and 69.1% (p < 0.05 for MI and angina patients)

*p < 0.05 for difference between groups.

CAD = coronary artery disease; CFR = coronary flow reserve ratio; LAD = left anterior descending; MI = myocardial infarction; MPI = myocardial perfusion imaging; NS = not significant; NTG = nitroglycerin; PET = positron emission tomography; SDS = summed difference score; SPECT = single-photon-emission computed tomography; SSS = summed stress score; Tc = technetium.

Table 2 **Summary of Studies That Evaluated the Effects of Statins on SPECT MPI**

Author, Year (Ref. #)	Patients	Treatment	Cholesterol Change (mg/dl)	Perfusion
Eichstadt et al., 1995 (100)	17 patients, high cholesterol, angina, and abnormal exercise TI-SPECT	Fluvastatin 40 mg 4 times daily for 6 weeks, increased to 40 mg twice daily if LDL decrease ≤30%	LDL 191 ± 26 (baseline) LDL 146 ± 28 (12 weeks) ($p < 0.001$)	Counts per matrix at 12 weeks: ↑ 30% in ischemic segments ($p < 0.001$) ↑ 5% in normal segments ($p < 0.005$)
Eichstadt et al., 2000 (101)	22 patients, high cholesterol, angina, and abnormal exercise TI-SPECT	Fluvastatin 40 mg 4 times daily for 6 weeks, increased to 40 mg twice daily if LDL decrease ≤30%	LDL 196 (baseline) LDL 145 (12 weeks) ($p < 0.001$) LDL 148 (24 weeks)	Counts per matrix at 12 weeks: ↑ 26% in ischemic segments ($p < 0.001$) ↑ 4% in normal segments ($p < 0.01$) Counts per matrix at 24 weeks: ↑ 29% in ischemic segments ($p < 0.001$) ↑ 4.4% in normal segments ($p < 0.01$)
Hosokawa et al., 2000 (102)	>50% CAD + prior MI or angina with abnormal exercise TI-SPECT: Statin group: 15 patients Control group: no lipid lowering	Statin group: simvastatin 5 mg 4 times daily Control group: no lipid lowering	Statin group: Non-HDL 197.7 ± 5.6 (baseline) Non-HDL 146.5 ± 5.7 (1 yr) ($p < 0.05$) Control group: Non-HDL 184.9 ± 9.0 (baseline) Non-HDL 194.3 ± 8.8 (1 yr) ($p < 0.05$)	Statin group: SSS 15.8 ± 3.6 SRS 13.1 ± 3.4 (baseline) SSS 11.7 ± 3.3 SRS 9.7 ± 3.0 (1 yr) ($p < 0.01$) Control group: SSS 13.4 ± 3.2 SRS 12.0 ± 2.8 (baseline) SSS 14.6 ± 2.0 ($p < 0.05$) SRS 12.9 ± 2.2 (1 yr)
Mostaza et al., 2000 (93)	20 patients with at least >1 vessel with >50% diameter stenosis, prior MI or stable angina with abnormal dipyridamole TI-SPECT, and average cholesterol on no lipid-lowering drugs (placebo-controlled with crossover design)	Pravastatin 20 mg 4 times daily for 16 weeks Placebo for 16 weeks	LDL 103 ± 23 after pravachol LDL 148 ± 25 after placebo ($p < 0.0001$)	SSS 5.9 ± 2.3 SDS 2.4 ± 2.2 SSS 7.2 ± 2.3 SDS 3.2 ± 1 ($p = 0.043$) $p = 0.012$ for SSS and $p = 0.043$ for SDS
Schwartz et al., 2003 (104)	25 patients with LDL ≥130 mg/dl, clinical CAD, and abnormal stress MPI underwent exercise or adenosine SPECT MPI at baseline, 6 weeks, and 6 months after lipid lowering	Pravastatin 40 mg 4 times daily for 6 months	LDL 134 ± 31 at baseline 91 ± 18 at 6 weeks ($p < 0.05$ vs. baseline) 96 ± 23 at 6 months ($p < 0.05$ vs. baseline)	SDS and percent LV perfusion defect 8.3 ± 4.6% and 25.5 ± 13.7% at baseline 6.5 ± 7.2% and 24.5 ± 14.1% at 6 weeks 5.0 ± 8.0% and 16.6 ± 13.8% at 6 months ($p < 0.05$ vs. baseline)
Manfrini et al., 2004 (103)	Post–single-vessel PCI with cholesterol <220 and not on antilipid drugs	Pravastatin 40 mg 4 times daily for 6 months Placebo	LDL 114 ± 17 to 101 ± 12 ($p < 0.05$) LDL 113 ± 7 to 113 ± 18	SDS 7.7 ± 2.8 at baseline to 0.3 ± 1.5* SDS 7.8 ± 2.7 at baseline to 3.9 ± 4.4

*$p < 0.05$ for difference between groups.

DM = diabetes mellitus; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular; MBP = myocardial blood flow; NCEP = National Cholesterol Education Program; PCI = percutaneous coronary intervention; SRS = summed rest score; TET = treadmill exercise testing; TI = thallium; other abbreviations as in Table 1.

without BBs (52,53). The patients exercised to the same work load before and after treatment, although their heart rates were lower (53). Intravenous propranolol administration to patients undergoing exercise MPI also decreased the perfusion defect size compared with placebo (50); the reduction in defect size was noted in the subgroup of patients who achieved the same double product with propranolol, suggesting that the effect may not entirely be related to the reduction in myocardial oxygen demand (50).

Similar BB effects were observed in patients who underwent exercise or dobutamine SPECT MPI. Chronic treatment decreased the rest and exercise defect severity compared with placebo (54). Acute propranolol administration before dobutamine MPI decreased the defect size and severity compared with the study without propranolol and normalized the scans in 23% of patients (55). The double product was significantly lower after intravenous propranolol despite higher infusion dobutamine doses (55).

Table 3   **Summary of Studies That Evaluated the Effects of Statins on PET MPI**

Author, Year (Ref. #)	Patients	Treatment	Cholesterol Change	Perfusion
Gould et al., 1994 (105)	12 patients with ≥1 vessel CAD (>50% diameter stenosis), stable angina, positive TET, and LDL ≥150 mg/dl Dipyridamole NH3-PET	3 months of NCEP step 2 diet and 20-mg lovastatin twice daily and 1 packet of cholestyramine, no-fat enteral diet, or total parenteral nutrition (lipid-free solution)	LDL (mg/dl) 213 ± 79 pre-treatment (p < 0.01) 151 ± 59 post-treatment 207 ± 67 post-washout (p < 0.01)	Dipyridamole/rest normalized counts Percent >2.5 SD: 22 ± 20% pre-treatment (p = 0.02) 13 ± 14% post-treatment 26 ± 22% post-washout period (p = 0.009)
Huggins et al., 1998 (112)	12 patients with ischemic heart disease and without tobacco abuse or DM Adenosine NH3-PET	Simvastatin 40 mg/day for 4.8 months	LDL (mg/dl) 171 ± 13 at baseline 99 ± 18 at 4.8 months (p < 0.001)	Hyperemic MBF of abnormal segments 1.8 ± 0.5 at baseline 2.5 ± 1.0 at 4.8 months (p < 0.01)
Baller et al., 1999 (113)	23 patients with angina, minimal CAD, elevated LDL, and abnormal CFR by dipyridamole NH3-PET	Simvastatin 20 mg 4 times daily for 6 months	LDL (mg/dl) 165 ± 34 at baseline 95 ± 26 at 6 months	CFR 2.2 ± 0.6 at baseline to 2.64 ± 0.6 (p < 0.01)
Guethlin et al., 1999 (114)	15 patients with angiographically documented multivessel CAD and LDL >160 mg/dl Adenosine NH3-PET	Fluvastatin 60 to 80 mg/day for 6 months	LDL (mg/dl) 181 ± 20 at baseline 114 ± 14 at 2 months (p < 0.05) 113 ± 17 at 6 months (p < 0.05)	Global CFR 2.5 ± 0.6 at baseline 2.7 ± 0.9 at 2 months (p = NS vs. baseline) 3.4 ± 1.0 at 6 months (p < 0.05 vs. baseline)
Yokoyama et al., 1999 (115)	27 hypercholesterolemic patients with >1 normal coronary artery on angiography Dipyridamole NH3-PET	Lipid-lowering drugs for 8 to 15 months	LDL (mg/dl) 173 ± 34.8 at baseline 123 ± 23.0 mg/dl at 8 to 15 months (p < 0.01)	CFR of normal coronary arteries 2.25 ± 0.77 at baseline 3.27 ± 1.69 at 8 to 15 months (p < 0.01)
Yokoyama et al., 2001 (116)	16 patients with familial hypercholesterolemia, no known CAD or angina symptoms, and normal TET Dipyridamole NH3-PET	Simvastatin 5 to 10 mg/day for 9 to 15 months	Total cholesterol (mg/dl) 277 ± 49 at baseline 205 ± 40.3 at 9 to 15 months (p < 0.01)	Global CFR 2.27 ± 0.63 at baseline 3.33 ± 1.19 at 9 to 15 months (p < 0.01)
Ling et al., 2005 (117)	72 patients with CAD and elevated LDL Dipyridamole Rb-PET	Simvastatin 20 mg 4 times daily (n = 23) for 8 weeks Pravastatin 40 mg 4 times daily (n = 24) for 8 weeks Placebo (n = 25)	LDL (mmol/l) 3.52 ± 0.6 to 1.88 ± 0.48 (p < 0.001) 3.5 ± 0.7 to 2.3 ± 0.6 (p < 0.001) 3.5 ± 0.5 to 3.8 ± 0.7	Global flow reserve/ segmental flow reserve 2.1 ± 0.6 to 1.9 ± 0.8/ 1.7 ± 0.6 to 1.7 ± 0.9 2.3 ± 1.1 to 1.6 ± 0.8/ 1.8 ± 0.7 to 1.8 ± 0.6 2.1 ± 0.6 to 2.3 ± 0.7/ 1.8 ± 0.6 to 2.1 ± 0.7

∗p < 0.05 for difference between groups.
  MBF = myocardial blood flow; other abbreviations as in Tables 1 and 2.

The effect of chronic atenolol use on dipyridamole SPECT MPI was assessed in a randomized, double-blind, crossover study that showed no difference in the perfusion defect size and severity between placebo and atenolol for the group as a whole, although one-third of patients had larger defects on atenolol than placebo (56). The acute administration of metoprolol before dipyridamole MPI decreased the sensitivity of CAD detection from 86% to 71% and reduced the extent and severity of ischemia by 25% to 30% compared with placebo (57).

Effects of BB on MBF. Because the effects of medications on myocardial perfusion might be explained by their effects on MBF, studies that examined such effects with either the PET or Doppler-wire method warrant a short discussion (Table 1).

The acute administration of metoprolol (50 mg orally given 12 h and 1 h before the study) before dipyridamole NH3-PET decreased resting MBF and increased hyperemic MBF, resulting in a significant increase in the coronary flow reserve ratio (CFR) compared with no BB administration (58). The chronic administration of BB increased CFR in stenotic vessels, but it did not affect the CFR in normal segments during adenosine NH3-PET (42). In an angioplasty model that used a Doppler wire to measure CFR, pre-treatment with intravenous metoprolol increased post-ischemic CFR (after 1 min of balloon occlusion) and post-adenosine CFR compared with no metoprolol pre-treatment (59).

Bottcher et al. (60) studied the effects of nitroglycerin, metoprolol (50 mg/day), and amlodipine (5 mg/day) in 49

Table 4	Summary of Experimental Data of Effects of Nitrates, Beta-Blockers, Calcium-Channel Blockers, and Lipid-Lowering Agents

Author, Year (Ref. #)	Study	Observation
Nitrates		
Cohen et al., 1973 (18)	Effect on myocardial function in dogs after coronary occlusion	Dilates coronary collaterals and increases collateral flow
Macho et al., 1981 (15)	Effect of coronary occlusion in dogs on flow, diameter, and resistance	Increases coronary cross-sectional area, decreases diastolic resistance, and has greater effect on large coronary arteries
Habazettl et al., 1990 (13)	Effect in dogs on coronary microvessel diameter and perfusion	Decreases resistance and increases large-vessel diameter; small-vessel dilation exceeds that of larger vessels only after high doses
Kanatsuka et al., 1992 (17)	Effect in dogs on microcirculation in ischemic zones	Dilates coronary microvessels distal to the stenosis, but perfusion remains constant; overall resistance does not change
Lacoste et al., 1994 (22)	Effect in pigs on thrombus formation	Decreases platelet aggregation to ADP and thrombin and decreases thrombus size
Salvemini et al., 1996 (21)	Effect in rats on in vivo thrombin-induced platelet aggregation	Enhances cyclo-oxygenase activity and inhibits platelet aggregation to adenosine diphosphate by 80%
Folts et al., 1991 (19)	Effect in dogs on platelet thrombus formation in coronary stenosis	Decreases platelet thrombus formation without affecting coronary flow
Muller et al., 2004 (118)	Effect in rabbits on aortic vascular superoxide, intimal lesion formation, and vasoreactivity	Inhibits the increase of vascular bioavailability of superoxide, prevents intimal lesion formation and endothelial dysfunction in hypercholesterolemia
Calcium-channel blockers		
Reimer et al., 1985 (64)	Myocardial protection in dogs after coronary occlusion/reperfusion	Reduces infarct size from 34% to 8%, decreases myocardial energy demand, and prevents depletion of ATP during ischemia
Tillmanns et al., 1991 (63)	Effect in rats on microcirculation	Increases diameter of larger coronary arterioles, increases myocardial phosphocreatine, and preserves ATP
Sassen et al., 1991 (65)	Effect in pigs on flow with occlusion/reperfusion	Increases flow, increases ADP and creatine phosphate, and reduces Ca_2+ overload
Park et al., 1996 (66)	Effect in pigs of repetitive ischemia	Attenuates myocardial stunning independent of hemodynamic changes
Ehring et al., 1997 (68)	Effect in dogs on myocardial blood flow, function, and infarct size with severe coronary stenosis	Decreases infarct size, improves recovery of stunned myocardium, and enhances myocardial blood flow
Folts et al., 1997 (67)	Effect in dogs on platelet aggregation	Prevents coronary thrombosis
Beta-blockers		
Matsuzaki et al., 1984 (44)	Effect in dogs with coronary stenosis on exercise-induced myocardial ischemia	Decreases HR, systolic pressure, and (+)dP/dt during exercise; improves function in ischemic zone, and increases endocardial-to-epicardial flow ratio
Grover et al., 1987 (43)	Effect in dogs with coronary occlusion on myocardial O_2 supply and demand	Improves subendocardial/subepicardial flow ratio in ischemic areas, increases myocardial O_2 extraction, and decreases O_2 consumption in ischemic regions
Guth et al., 1987 (41)	Effect in dogs with coronary stenosis on exercise-induced myocardial ischemia and regional dysfunction	Decreases HR and increases ischemic wall function; preserves regional blood flow
Liu et al., 1991 (46)	Effect in rats of 3 different beta-blockers on membrane phospholipid integrity after ischemia/reperfusion	Decreases lipid peroxidation, reduces accumulation of free fatty acids, decreases myocardial creatine kinase release, enhances recovery of coronary flow, and preserves membrane phospholipids
Feuerstein et al., 1993 (49)	Effect in rats, minipigs, and dogs on infarct size	Reduces infarct size and inhibits lipid peroxidation in a dose-dependent manner, suppresses superoxide generation, and scavenges oxygen free radicals
Zmudka et al., 1998 (45)	Effect in dogs on myocardial O_2 consumption and metabolism after coronary artery occlusion	Reduces infarct size, increases coronary collateral flow, decreases myocardial oxygen consumption, and preserves myocardial uptake of lactate and nonesterified fatty acid
Schwarz et al., 2003 (48)	Effect in rats on infarct size and apoptosis in an infarct model	Reduces infarct size and apoptosis
Monteiro et al., 2003 (47)	Effect in rats on mitochondrial function during ischemia	Increases mitochondrial energy charge, preserves electrical potential, and enhances mitochondrial function

patients with severe CAD (>70% stenosis) who randomly underwent dipyridamole MPI with NH3-PET while on and off medications (>5 half lives). Nitroglycerin (n = 25) increased the resting MBF. Unlike the prior studies, this study showed that BBs (n = 14) decreased the resting and hyperemic MBF in stenosis and normal segments with no change in CFR (60). Calcium-channel blockers (10 patients) did not have a significant effect on resting or dipyridamole-induced hyperemic MBF (60). In contrast, Zervos et al. (61) reported that nifedipine increased MBF

(by PET) in normal segments as well as in segments with mild, moderate, and severe stenoses, though the improvement was to a lesser extent as stenosis severity increased.

In summary, BBs improve the perfusion pattern of exercise and dobutamine MPI, but the results are inconsistent with vasodilator MPI. The changes are likely caused by alterations in MBF. The implication of such results is that BBs are likely to decrease the sensitivity of exercise or dobutamine MPI, but their effects on the sensitivity of vasodilator MPI remains unclear. The latter might depend

Table 4 **Continued**

Author, Year (Ref. #)	Study	Observation
Lipid-lowering drugs		
Bellosta et al., 1998 (70)	Effect in mouse on the activity of MMP-9 in macrophages	Inhibits MMP-9 activity in a dose-dependent manner
Lefer et al., 1999 (72)	Effect in rats on neutrophil-mediated cardiac injury	Improves coronary flow, enhances endothelial release of nitric oxide, and reduces PMN accumulation
Fukumoto et al., 2001 (75)	Effect in rabbits on interstitial collagen gene expression and MMP levels	Decreases MMP-1, -3, and -9 expression by macrophages
Bonetti et al., 2002 (82)	Effect in pigs on myocardial perfusion and microvascular permeability	Increases myocardial perfusion and preserves microvascular permeability index independent of lipid lowering
Wilson et al., 2002 (80)	Effect in pigs on coronary vaso vasorum neovascularization	Attenuates hypoxia in the coronary artery wall and decreases vaso vasorum neovascularization in the absence of cholesterol lowering
Jones et al., 2002 (77)	Effect in mice on endothelial nitric oxide production and reperfusion	Increases nitric oxide production and nitric oxide synthase messenger ribonucleic acid levels, and reduces myocardial necrosis by 40%
Ikeda et al., 2003 (73)	Effect in rats on ischemic and reperfused hearts perfused with PMNs	Reduces PMN adherence to vascular endothelium and PMN infiltration into post-ischemic myocardium; improves left ventricular function
Boodhwani et al., 2006 (71)	Effect in pigs on endothelial function in chronic myocardial ischemia	Improves endothelial dysfunction; increases phosphorylation of Akt, decreases vascular endothelial growth factor, and increases expression of endostatin
Zhao, 2006 (81)	Effect in pigs on restoration of blood flow after coronary occlusion	Increases coronary blood flow, decreases area of no-reflow, and reduces infarct size

ADP = adenosine diphosphate; ATP = adenosine triphosphate; Ca^{2+} = intracellular calcium; HR = heart rate; MMP = matrix metalloproteinasese; PMN = polymorphonuclear leucocytes.

on patient selection (extent and severity of CAD) as well as the dose of BBs. A reduction in defect size might be more common than complete normalization of the perfusion pattern.

CCBs

Experimental studies. The primary benefit of CCBs seems to be a reduction in myocardial oxygen demand, which is achieved by decreasing arterial tone, peripheral vascular resistance, intraventricular pressure, and wall stress (10,62).

Calcium channels consistently open after depolarization, resulting in an increase in intracellular calcium, which forms a complex with calmodulin, thereby activating myosin light chain kinase. Activated myosin light chain kinase phosphorylates myosin light chains, resulting in myosin–actin interaction, namely smooth muscle cell contraction (10). After CCBs bind to the calcium channel, these channels open infrequently and dramatically reduce the influx of intracellular calcium. This results in long-lasting smooth muscle relaxation, which leads to coronary vasodilation and a decrease in systemic vascular resistance. Moreover, cardiomyocytes depend on intracellular calcium for excitation–contraction coupling, and CCBs further reduce oxygen demand in a dose-dependant manner by decreasing contractility and heart rate (nondihydropyridine CCBs) (10,62).

Calcium-channel blockers also enhance myocardial perfusion through their effects on myocardial microcirculation and metabolism (63,64). They may improve coronary flow in CAD by selectively dilating larger arterioles (63).

Although CCBs decrease myocardial oxygen demand indirectly though a reduction in heart rate and contractility, these agents also directly decrease myocardial energy requirements (64). Ischemia leads to membrane depolariza-

tion and a marked increase in intracellular calcium. This stimulates adenosine triphosphate-consuming enzymes, taxing an already depleted energy reserve (10). However, CCBs increase myocardial phosphocreatine and preserve adenosine triphosphate during ischemia (63). Nisoldipine significantly increases sarcoplasmic reticular intracellular calcium pump activity and slightly augments the rate of intracellular calcium uptake in post-ischemic myocardium (65).

Calcium-channel blockers enhance use of free fatty acids in reversibly ischemic myocardium and attenuate myocardial stunning independent of hemodynamic changes (63,66). Pre-ischemic nisoldipine administration enhances the recovery of stunned myocardium after transient coronary artery occlusion. Thus, CCBs may provide cardiovascular protection by attenuating calcium overload during ischemia independent of hemodynamic changes (66).

Calcium-channel blockers inhibit platelet aggregation and thrombus formation, which may improve myocardial perfusion (10,62,67). In fact, amlodipine completely prevented coronary platelet aggregation even after epinephrine administration in a model of experimental coronary artery thrombosis (67).

Calcium-channel blockers may potentially increase myocardial perfusion by preventing coronary spasm and by improving collateral flow (64). In a canine model of severe coronary artery stenosis, nifedipine increased coronary flow in areas of ischemia by combating the antagonism of alpha-adrenergic coronary vasomotor tone during exercise (68). Another large experimental model demonstrated that pre-treatment with verapamil reduced the size of subendocardial infarcts in the ischemic territory and preserved regional function (64,68).

Clinical studies. Different CCB doses, CCB types, and modes of administration were used to study the effects of

Table 5	Factors That Affect Image Analysis for Effects of Medications on MPI

A. Serial testing
  1. One intervention versus another
  2. Before and after intervention
  3. Interval testing
  4. Single center versus multicenter
B. Issues to be considered
  1. Global qualitative
    a. Normal
    b. Abnormal
      i. Scar
      ii. Ischemia
  2. Global quantitative
    a. Total perfusion abnormality
    b. Reversible abnormality
    c. Extent versus severity
    d. Discrete or continuous change
      i. Better/worse/same
      ii. Percent change
  3. Regional quantitative change
    a. Total abnormality in each vascular territory
    b. Reversible abnormality
C. Factors affecting interpretation
  1. Technical
    a. Image quality
    b. Image protocol
    c. Doses of tracers
    d. Stress test
  2. Biological: day-to-day variation
  3. Repeatability
    a. Percent abnormal studies
    b. Sequential reading
    c. Side-by-side reading
      i. Biases
      ii. Blinded
      iii. Visual
      iv. Automated
      v. Group results versus individual patient

Adapted and reprinted with permission from Iskandrian et al. (6).

CCBs on exercise MPI (Table 1). The acute administration of nifedipine before exercise planar MPI improved perfusion (defined as >20% increase) in approximately one-half of patients and in one-fourth of segments compared with no CCB administration. The chronic administration of nifedipine before exercise planar MPI decreased ischemia, as evidenced by an increase in percent counts in ischemic zones compared with no CCB administration (27).

The chronic administration of nifedipine and nicorandil in 2 separate studies before exercise SPECT reduced the defect extent (28) and severity (69) and decreased the extent of ST-segment depression (28).

In summary, the limited available data suggest that CCBs improve myocardial perfusion during exercise in patients with CAD. The effects on vasodilator MPI have not been studied. The same general conclusions may be implied from

these data on the effects of CCBs on sensitivity of stress MPI as with BB.

Lipid-Lowering Agents

Experimental studies. The major cardiovascular benefit of statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) is the inhibition of cholesterol synthesis in the liver. However, additional mechanisms for the vascular protective effects exist (70–75). Statins improve endothelial function and preserve coronary perfusion independent of their reduction in cholesterol (70–75). They increase smooth muscle relaxation, decrease oxidative stress, prevent vascular inflammation, decrease inflammatory cell and platelet adhesion to the endothelial wall, reduce platelet aggregation and thrombosis, stabilize plaque, and possibly promote angiogenesis (76).

Statins increase nitric oxide bioavailability through the activation of Akt (71,72,77,78). Akt induces endothelial nitrous oxide synthase production and enhances its activity (71,72,77,78). Nitrous oxide synthase decreases myocardial oxygen demand through vasorelaxation and a resultant reduction in left ventricular wall tension (10,71). Statins also increase vascular smooth muscle relaxation in hyperlipoproteinemic rabbits and in obese Zucker rats by inhibiting Rho, a small GTP-binding protein (71). Rho enhances phosphorylation of myosin light chains, which induces myosin–actin interaction and smooth muscle cell contraction (71).

Statins stimulate nitric oxide synthase activity, and this prevents the expression of adhesion molecules, cytokines, and superoxides inhibiting neutrophilic infiltration and myocyte injury associated with ischemia and reperfusion (72–74,78). In normocholesterolemic rats, simvastatin protected against vascular inflammation, and nitric oxide synthase attenuated polymorphonuclear leukocyte adherence and minimized capillary plugging by inflammatory cells and platelets (71–73,78). In fact, polymorphonuclear leukocytes release cytotoxic mediators such as oxygen-derived free radicals, inflammatory cytokines, and proteases (72). Statins also stimulate the synthesis of heme oxygenase-1 in macrophages, endothelial cells, and vascular smooth muscle cells, and heme oxygenase-1 has anti-inflammatory properties after ischemia-reperfusion injury, limiting tissue death (79). Statins also protect against hypoxia in the walls of coronary arteries by attenuating vasa vasorum neovascularization independent of cholesterol lowering (80). Vasa vasorum are vessels located in the adventitia that provide nourishment to coronary arteries. Vasa vasorum neovascularization is directly related to atherosclerosis, and it precedes plaque progression (80). Hypercholesterolemia and coronary wall hypoxia promote the expression of hypoxia-inducible factor and proangiogenic factors such as matrix metalloproteinases and vascular endothelial growth factor in coronary artery walls.

High-dose atorvastatin improves endothelial dysfunction in hypercholesterolemic swine without promoting angiogenesis. Atorvastatin increases phosphorylation of Akt,

blunts the expression of vascular endothelial growth factor, and augments the secretion of endostatin, an antiangiogenic protein (71). Endostatin prevents endothelial cell growth and migration and blunts the secretion of hypoxia-inducible factor (71). Plaque stability also depends on their collagen content, and statins have been shown to reduce matrix metalloproteinase expression in atheroma, decrease intimal smooth muscle cells, and reduce collagen gene expression (70,75). Matrix metalloproteinases are secreted by macrophages and weaken the fibrous cap of atherosclerotic plaque, resulting in plaque rupture (70,75,80). Statins decrease myocardial no-reflow after ischemia and reperfusion by opening mitochondrial K_{ATP} channels (78,81). There is evidence that pre-treatment with statins might precondition and protect against myocardial no-reflow mediated by activation of mitochondrial K_{ATP} channels, and nitric oxide plays an integral role in activating these channels (78). By opening mitochondrial K_{ATP} channels, the balance between K+ uniport and K+/H+ antiport shifts resulting in a net K+ uptake. This leads to matrix swelling and up-regulates electron transport (78). As a result, mitochondrial K_{ATP} channel activation improves matrix integrity, promotes mitochondrial membrane depolarization, and inhibits the production of reactive oxygen species (78).

Independent of lipid-lowering, chronic treatment with simvastatin preserves myocardial perfusion and coronary microvascular integrity as measured by the permeability index (82). Adenosine and dobutamine markedly increased myocardial perfusion in pigs receiving normal diets and high-cholesterol diets with simvastatin (82). In contrast, the changes in myocardial perfusion were significantly blunted in the high-cholesterol group that did not receive statin therapy (82). During stress, the permeability index was not changed in the normal diet or high-cholesterol diet plus simvastatin group, but the permeability index was significantly increased in the pigs receiving a high-cholesterol diet only (82). These findings suggest that statins improve myocardial perfusion by preserving endothelial function (82).

Clinical studies. Lipid-lowering medications, particularly statins, have been shown to reduce cardiovascular events in primary and secondary prevention trials by 24% to 37% (83). An additional 11% to 21% reduction was achieved with intensive high-dose versus moderate-dose statin therapy (84–87). Although statins may produce a regression or halting of the progression of atherosclerosis as assessed by coronary angiography and intravascular ultrasound, the degree of regression is slight compared with the substantial improvement in clinical outcomes (88,89). The improved clinical outcomes are likely related to plaque stabilization and protection against disruption. Endothelial-dependent coronary vasodilation abnormalities usually precede clinical atherosclerosis and the development of stenoses on coronary angiography and can be assessed by MPI (90,91). The impaired endothelial function is mediated by diminished release of nitric oxide or its increased metabolism, and the reduction in nitric oxide leads to impairment of local

thromboprotective mechanisms and promotion of inflammation and vasospasm (92). Statins activate nitric oxide synthase expression to increase nitric oxide production and inhibit endothelin expression to decrease endothelin-1 production, a potent vasoconstrictor and promoter of inflammation and atherosclerosis (93). Thus, the effects of statin therapy on the results of MPI are caused by beneficial effects on vasomotor abnormalities by improving endothelial integrity and function, decreasing vascular inflammation, improving intrinsic coronary wall elasticity, improving coronary reserve and arterial wall responsiveness to vasodilators, and to a lesser extent by mild regression of fixed stenoses (91,94).

Effects of lipid-lowering agents on MBF. The effect of lipid lowering on the coronary vasomotor response to acetylcholine (endothelial-dependent vasodilator) or papaverine (endothelial-independent vasodilator) was assessed with different lipid-lowering agents. Acetylcholine vasoconstricts the coronary artery in the presence of endothelial dysfunction. A cholesterol-lowering diet and cholestyramine for 6 months abolished the acetylcholine-induced vasoconstriction that occurred at baseline before therapy (95). Treatment with pravastatin for 6 ± 3 months ameliorated the acetylcholine-induced vasoconstriction of the epicardial arteries that was present at baseline and increased the coronary blood flow compared with baseline (96). The responses to papaverine and nitrates were similar between the baseline studies and the follow-up studies after treatment with pravastatin, suggesting that the effect of statins is on endothelial-dependent vasodilation (96). Acetylcholine-mediated vasodilation was not affected after treatment with lovastatin for 12 days, but significantly improved after 5.5 months of treatment with lovastatin compared with baseline (97). The improvement in endothelial function lagged behind the improvement of low-density lipoprotein (LDL) levels that occurred in a matter of days to weeks after initiation of therapy. Improvement in acetylcholine-mediated endothelial vasodilation was also seen after 1 year of treatment with lovastatin and cholestyramine and with lovastatin and probuchol (antioxidant effect) (98). The ameliorating effects of lipid lowering on acetylcholine-mediated vasoconstriction was not seen after treating patients with mild CAD and mildly elevated lipids with 6 months of simvastatin (99). However, the results of this study differ from other cited studies, which may be explained by technical factors, study design, baseline characteristics, differences in lipid-lowering regimens, and other unaccounted medications that may affect endothelial function. The effects of lipid lowering on endothelial function were more pronounced in patients who had more than mild CAD and more than mild lipid abnormalities.

Effects of lipid-lowering therapy on MPI by SPECT. The alteration in MBF would suggest that lipid-lowering therapy and especially statins may have an important effect on MPI. Several studies showed a decrease in the size of reversible defects by exercise MPI after lipid-lowering

therapy (Table 2). Treatment with fluvastatin for at least 6 weeks to reach at least 30% LDL lowering decreased the exercise-induced ischemia that was seen on baseline MPI (100). Compared with baseline, perfusion in ischemic segments improved by 26% at 12 weeks and by 29% at 24 weeks; no correlation was present between change in LDL and change in perfusion (101). The extent and severity of ischemia on exercise MPI improved significantly after treatment with 5 mg simvastatin for 1 year compared with baseline, whereas it worsened in a group of patients with similar baseline characteristics who were treated with placebo (102). Similar improvement was noted in the resting perfusion, possibly because of improvement in perfusion of hibernating or repetitively stunned myocardium (102).

In a study that randomized patients who underwent successful single-vessel percutaneous coronary intervention (PCI) and who had cholesterol <220 mg/dl without treatment to placebo (n = 31) or to treatment with 40 mg pravastatin per day, reversible perfusion defects on exercise MPI occurred in two-thirds of patients of both groups at 2 weeks but became significantly less frequent at 6 months in the pravastatin group (103). The decrease in LDL correlated with a lower incidence of perfusion defects in the pravastatin group (r = 0.46, p = 0.005) (103).

Treatment with pravastatin for 16 weeks improved the defect size and severity that was seen on baseline dipyridamole MPI (93). Treatment with pravastatin followed by exercise or adenosine MPI at 6 weeks and 6 months improved perfusion defect size from 26 ± 14% at baseline to 25 ± 14% at 6 weeks and to 17 ± 4% at 6 months (p < 0.05 vs. baseline for both) (104). The stress perfusion improved in 48% of patients at 6 months (104). This improvement in MPI lagged behind the lowering of LDL levels, and changes in lipid levels did not reliably predict changes in myocardial perfusion at 6 weeks or at 6 months (104).

Effects of lipid-lowering therapy on MPI by PET. The effects of lipid lowering on MPI by PET were first studied by Gould et al. (105) in a study design that included diet and lipid-lowering treatment. Serial dipyridamole NH3-PET studies were performed and assessed quantitatively by measuring the ratio of stress to rest normalized counts. The stress defect decreased from 22 ± 20% before to 13 ± 14% after treatment (p = 0.02) and increased again to 26 ± 22% after discontinuation of active treatment. The beneficial effects of statins were further confirmed in subsequent studies that used dipyridamole or adenosine PET.

Treatment with simvastatin and pravastatin failed to show improvement in CFR by rubidium PET but not by N-13 ammonia PET, most likely because N-13 ammonia PET is more accurate than rubidium (105–110) (Table 3).

The effect of intense life-style modification and pharmacologic lipid treatment on dipyridamole NH3-PET was studied in 409 patients with stable CAD who underwent stress PET at baseline and after 2.6 years (106). Patients were categorized prospectively and blindly into 3 treatment strategies: 1) poor treatment by diet or lipid drugs, or

continued active smoking; 2) moderate treatment on the American Heart Association diet and lipid-lowering drugs or a strict low-fat diet (<10% of calories) without lipid drugs; and 3) maximal treatment with diet <10% of calories as fat, regular exercise, and lipid-active drugs dosed to target goals of LDL <90 mg/dl, high-density lipoprotein >45 mg/dl, and triglycerides <100 mg/dl (106). The size and the severity of the perfusion defect significantly decreased in the maximal treatment group and increased in the moderate and poor treatment groups at 2.6 years of follow-up (p = 0.001) (106). However, this study was not randomized, and medications such as BBs, aspirin, and angiotensin-converting enzyme inhibitors were different in the 3 groups.

In summary, lipid-lowering medications improve the perfusion pattern of exercise and vasodilator MPI. This improvement may occur as early as 2 months as shown in some studies, but occurs more definitely beyond 6 months of lipid lowering. Because most patients with known or suspected CAD are on statin therapy, it is difficult to ascertain the relative importance of the other cardiac medications, especially during vasodilator MPI. The PET quantitative data clearly support the notion of improvement in hyperemic MBF and even resting MBF (based on patient selection) and provide confirmatory data to the qualitative MPI data by either SPECT or PET.

Effects of Combination of Antianginal Medications

The effects of combined anti-ischemic medications (BBs, CCBs, nitrates, and stains) were examined in 2 studies, and both showed a decrease in perfusion defect size and severity (11,107) (Table 6). Patients who remained clinically stable had a greater reduction in ischemic perfusion defect score (−13 ± 9%) than those who had a recurrent cardiac event (−5 ± 7%; p < 0.02). Event-free survival at 12 ± 5 months was 96% in patients who had a significant (≥9%) reduction in perfusion defect score compared with 65% in those who did not (p = 0.009) (107). The hypothesis-generating pilot study by Dakik et al. (107) was the basis for the INSPIRE (Adenosine Sestamibi Post-Infarction Evaluation) trial.

The INSPIRE trial. The INSPIRE trial prospectively randomized 205 stable survivors of acute myocardial infarction to a strategy of intensive medical therapy compared with revascularization for the suppression of adenosine-induced ischemia on MPI (108). All patients had large total (≥20%) and reversible perfusion defects (≥10%) and left ventricular ejection fraction ≥35%. Patients were then randomized to a strategy of intensive anti-ischemic medical therapy (group 1) or a strategy of coronary angiography with the intent of revascularization (group 2). Baseline and follow-up adenosine MPI studies were performed at a median of 10 and 62 days after myocardial infarction, respectively. Cross-over from medical therapy to revascularization occurred in 26% of patients and from the revascularization strategy to medical therapy in 23% of patients. Of

Table 6   Summary of Studies That Evaluated the Effects of Combination Antianginal Medications on Stress SPECT

Author, Year (Ref. #)	Patients	Treatment	Testing	Perfusion
Sharir et al., 1998 (11)	26 patients with ≥1 reversible perfusion defects on first dipyridamole Tl-SPECT study while off antianginal medications underwent a second dipyridamole Tl-SPECT on antianginal medications	Off antianginal medications: 48 h for CCB and BB and for at least 24 h for nitrates On antianginal medications: CCB (81%), nitrates (73%), BB (31%), and >1 antianginal medication (77%)	Off antianginal medications On antianginal medications	SSS = 24 ± 10; SRS = 15 ± 8 SSS = 9 ± 11; SRS = 11 ± 9 (p = 0.01 for summed stress score and 0.04 for summed rest score)
Dakik et al., 1998 (107)	44 stable survivors of acute MI who had a large total (≥20% of left ventricular myocardium) and ischemic (≥10%) perfusion defect size on baseline adenosine Tl-SPECT	Maximum tolerated doses of metoprolol, nitrates, and diltiazem: 73% were on 2 and 27% on 3 medications PCI : 16% were on any maximal antianginal medication Randomized study	Baseline vs. intensive medical therapy Baseline vs. PCI: 19 patients (treatment test performed at 43 ± 26 days from baseline test)	Total perfusion/ischemic defect size (%) 38 ± 13/22 ± 12 to 26 ± 16/10 ± 10 (p < 0.0001) 35 ± 12/18 ± 6 to 20 ± 16/6 ± 7 (p < 0.0001)

BB = beta-blocker; CCB = calcium-channel blocker; other abbreviations as in Tables 1 and 2.

group 2, 81% of patients had PCI; 70% of patients in group 1 and 36% in group 2 were on 2 or more antianginal medications (p < 0.05). Significant reductions in reversible defect size (−15 ± 9% vs. −16.2 ± 9%; p = NS) and total defect size (−16.2 ± 10% vs. −17.8 ± 12%; p = NS) were noted in groups 1 and 2, respectively. The incidence of death or nonfatal reinfarction at 1 year was 7.9% in group 1 and 6.7% in group 2 (p = NS) (108). Of note, lipid-lowering therapy was used in both groups. An example of the effects of combination therapy is shown in Figure 1.

The COURAGE nuclear substudy. The nuclear substudy of the COURAGE (Results from Clinical Outcomes Utilizing Revascularization and Aggressive Guideline-Driven Drug Evaluation) trial recruited 159 patients who were treated with PCI plus optimal medical therapy and 155 patients who were treated with optimal medical therapy alone (2). The patients had a baseline stress MPI and a repeat stress MPI after 6 to 18 months of treatment. The results showed that PCI added to optimal medical treatment was more effective in reducing ischemia and improving angina than optimal medical treatment alone, particularly in patients with moderate-to-severe pre-treatment ischemia. Improvement in the ischemic burden on stress MPI occurred in 33% of patients in the PCI plus optimal
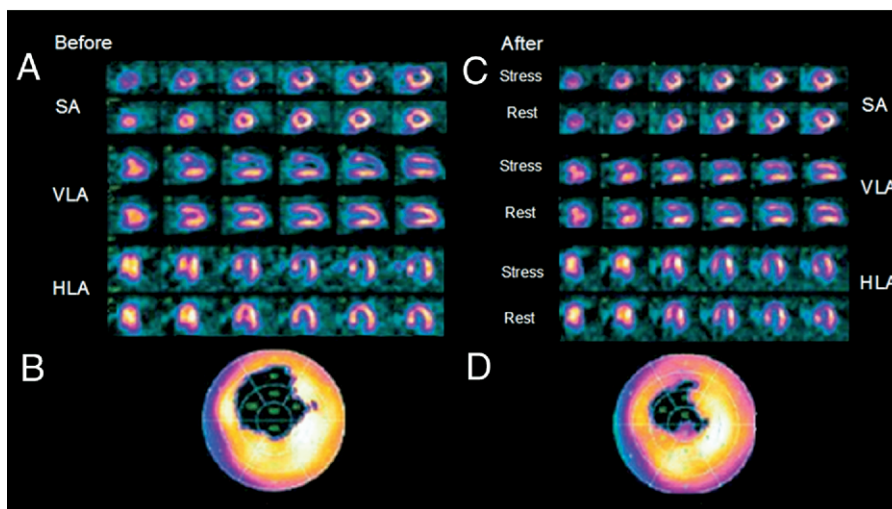

Figure 1   Baseline and Follow-Up Stress/Rest SPECT Sestamibi MPI After Medical Therapy

(A) A patient's baseline stress/rest SPECT sestamibi perfusion images showing large ischemia of the left anterior descending artery territory; the **top rows** show stress images and the **bottom rows** show rest images. **(B)** Polar maps estimated the extent of total ischemia to be 31% of left ventricular myocardium. The left ventricular ejection fraction was 62% by gated SPECT. **(C)** SPECT sestamibi MPI at 6-month follow-up with maximal medical therapy including statin, beta-blockers, and nitrates. The ischemia (same format as **A**) is less. **(D)** Polar maps estimated extent of total abnormality to be 21%, ischemia 16%, and scar 5%. The left ventricular ejection fraction was 67%. HLA = horizontal long axis; MPI = myocardial perfusion imaging; SAX = short axis; SPECT = single-photon emission computed tomography; VLA = vertical long axis.

medical therapy arm, compared with 19% of patients in the optimal medical therapy alone group (2). Patients with moderate to severe pre-treatment ischemia had a 78% improvement in ischemia, compared with 52% in those who had mild pretreatment ischemia (p = 0.007) (2). Furthermore, ischemia reduction was associated with a lower risk of death/myocardial infarction, whereas residual ischemia was associated with a higher risk of death/myocardial infarction regardless of the mode of treatment (2). There was a graded relationship between event risk and residual ischemia extent and severity. Death or MI occurred in 0% of patients with no ischemia and in 39.3% of patients with ≥10% ischemic myocardium on follow-up MPI (2).

Implications of Use of Cardiac Medications in Stress MPI

The cumulative data show that nitrates, first-generation CCBs, BBs, and especially statins modify results of stress MPI (especially exercise) by decreasing the extent and severity of reversible ischemia or even by eliminating ischemia completely in some patients. Nevertheless, the current American College of Cardiology/American Heart Association guidelines recommend that cardiac medications should not be discontinued before stress testing because of the fear of ischemic events (109,110). Furthermore, it is unlikely that discontinuation of statins for a day or two would nullify the protective effects. It should be noted that in research, unlike clinical studies, most of these medications are used in maximally tolerated doses. The effect of smaller doses is not clear, but it would presumably be less evident. The SPECT MPI appropriateness criteria and guidelines (111) suggest that stress MPI is most beneficial in patients with intermediate pre-test likelihood of CAD, and hence conceivably in such patients the detection of CAD, especially those with mild ischemia, may be masked by such medications or underestimated. For diagnostic purposes, it might be necessary to repeat the test after all medications are discontinued for a reasonable amount of time. On the other hand, the information provided by MPI while patients are on medications provides powerful prognostic data, as shown from multiple databases as well as prospective studies such as INSPIRE (in patients with acute coronary syndromes) and COURAGE (in patients with stable CAD). As such, results of stress MPI can be used to monitor therapy and gauge its success.

Reprint requests and correspondence: Dr. Todd A. Dorfman, Division of Cardiovascular Diseases, The University of Alabama–Birmingham, LHRB 306, 1530 3rd Avenue South, Birmingham, Alabama 35294-0007. E-mail: tdorfman@cardmail.dom.uab.edu.

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