Clinical Investigations ▬▬▬

Changes in Myocardial Perfusion Abnormalities by Positron Emission Tomography After Long-term, Intense Risk Factor Modification

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Objective.—To quantify changes in size and severity of myocardial perfusion abnormalities by positron emission tomography (PET) in patients with coronary artery disease after 5 years of risk factor modification.

Design.—Randomized controlled trial.

Setting.—Outpatient community setting.

Intervention.—Randomization of patients to risk factor modification consisting of very low-fat vegetarian diet, mild to moderate exercise, stress management, and group support (experimental group, n=20) or to usual care by their own physicians, consisting principally of antianginal therapy (control group, n=15).

Main Outcome Measures.—Quantitative coronary arteriography and PET at baseline and 5 years after randomization. Automated, objective measures of size and severity of perfusion abnormalities on rest-dipyridamole PET images and of stenosis severity on arteriograms were made by computer algorithms.

Results.—Size and severity of perfusion abnormalities on dipyridamole PET images decreased (improved) after risk factor modification in the experimental group compared with an increase (worsening) of size and severity in controls. The percentage of left ventricle perfusion abnormalities outside 2.5 SDs of those of normal persons (based on 20 disease-free individuals) on the dipyridamole PET image of normalized counts worsened in controls (mean±SE, +10.3%±5.6%) and improved in the experimental group (mean±SE, −5.1%±4.8%) (P=.02); the percentage of left ventricle with activity less than 60% of the maximum activity on the dipyridamole PET image of normalized counts worsened in controls (+13.5%± 3.8%) and improved in the experimental group (−4.2%±3.8%) (P=.002); and the myocardial quadrant on the PET image with the lowest average activity expressed as a percentage of maximum activity worsened in controls (−8.8%±2.3%) and improved in the experimental group (+4.9%±3.3%) (P=.001). The size and severity of perfusion abnormalities on resting PET images were also significantly improved in the experimental group as compared with controls. The relative magnitude of changes in size and severity of PET perfusion abnormalities was comparable to or greater than the magnitude of changes in percent diameter stenosis, absolute stenosis lumen area, or stenosis flow reserve documented by quantitative coronary arteriography.

Conclusions.—Modest regression of coronary artery stenoses after risk factor modification is associated with decreased size and severity of perfusion abnormalities on rest-dipyridamole PET images. Progression or regression of coronary artery disease can be followed noninvasively by dipyridamole PET reflecting the integrated flow capacity of the entire coronary arterial circulation.

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LIPID-LOWERING trials in patients with coronary atherosclerosis have demonstrated no progression or partial regression of coronary artery stenoses by coronary arteriography compared with progression of stenosis severity in controls treated with standard therapy.[1-24] However, these regression trials share several common limitations, including the following: the degree of regression was anatomically modest, being 5% to 10% diameter stenosis units; percent diameter stenosis is poorly related to flow capacity of coronary arteries or coronary flow reserve[4,25-32]; progression or regression of coronary artery stenoses may be associated with complex shape changes or remodeling,[4] in which the integrated hemodynamic effects of percent narrowing, absolute arterial lumen area, and length are not accounted for by any single geometric dimension such as percent stenosis[4,25-32]; and quantifying single focal stenoses on coronary arteriograms does not account for multiple stenoses, diffuse atherosclerosis, or the associated vasomotor abnormalities frequently present[33-35] and therefore does not reflect the perfusion capacity of the entire integrated coronary arterial circulation affected by atherosclerosis.

Although several lipid-lowering trials have demonstrated only modest reduction in percent diameter narrowing in treated vs control groups, these studies have reported a proportionately greater decrease in cardiac events in treated groups.* In view of current widespread interest in the noninvasive management of coronary atherosclerosis by cholesterol-lowering drugs, diet, exercise, and behavioral interventions, the potential impact of these trials on clinical practice is substantial, but data on changes in

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*References 2, 5, 11, 14, 15, 17-19, 22, 24.

myocardial perfusion abnormalities corresponding to the observed arteriographic changes are lacking. Accordingly, we measured the size and severity of myocardial perfusion abnormalities by positron emission tomography (PET) at rest and after dipyridamole stress at baseline and at an average follow-up of 5 years in patients with coronary artery disease (CAD) randomized to the control group or to the experimental group undergoing intense risk factor modification.

METHODS

Study Patients

Patients selected for participation in the risk modification program were men and women, 41 to 70 years old, who had CAD documented by arteriography, had no recent myocardial infarction, were not taking lipid-lowering drugs, had left ventricular ejection fraction greater than 25%, and resided in the greater San Francisco area of California. Individuals in each group gave informed consent and were randomized after we obtained baseline quantitative coronary arteriography but before other baseline measurements.[1,4]

Modification of risk factors has been described previously[1,4] and consisted of a low-cholesterol (<5 mg/d), low-fat (<10% of total energy intake) vegetarian diet with 15% protein and 75% complex carbohydrate augmented with vitamin B_{12}.[1,4] Patients stopped smoking, practiced stress management techniques for 1 hour daily, and participated in mild to moderate aerobic exercise 3 hours per week. Adherence to the program was quantified by a score reflecting a 3-day diet diary, an exercise and stress management diary, and confirmation of smoking cessation by plasma cotinine concentration. A total score of 1.0 indicated 100% adherence to the recommended lifestyle changes, whereas a score of zero indicated no adherence. A score greater than 1.0 indicated that patients did more than was recommended.

Quantitative Coronary Arteriography

Initial and follow-up coronary arteriograms were performed using the standard percutaneous femoral approach. Detailed records of the view angles, x-ray exposures, image intensifier, x-ray tube, patient distances, and reference catheter dimensions were maintained. These same characteristics were used in follow-up arteriograms to reproduce views and exposures as closely as possible. Angiograms were analyzed simultaneously in pairs by a technician unaware of clinical data or group assignment using automated border recognition and stenosis analysis techniques to avoid the potential bias, imprecision,

and uncertainties of visual interpretation. The primary stenosis dimensions measured by the automated arteriographic program previously described[1,4,25-29] include proximal diameter and cross-sectional lumen area, minimal diameter and area, distal diameter and area, the exit angle and exit shape effects, and calculated measures of severity, including percent diameter stenosis, percent area narrowing, integrated length-area effects, and stenosis flow reserve. This program has been validated in three separate experimental studies,[26-28] applied in humans,[1,4,33,36-40] and used routinely in approximately 5000 clinical arteriograms in our laboratory. The 95% confidence interval for stenosis flow reserve is ±0.66, with a reproducibility of primary dimensions of ±3% to ±5%.[1,4,25-29]

PET Imaging

As previously described,[36-43] PET imaging of myocardial perfusion was performed at rest and after administration of dipyridamole. Fluoroscopy was used to mark the cardiac borders for patient positioning. The PET imaging was performed using the University of Texas–designed cesium fluoride, multislice tomograph with a reconstructed resolution of 12 mm full width at half maximum (FWHM) in plane and 14 mm FWHM axially. Transmission images were obtained to correct for photon attenuation using the segmented attenuation correction method.[44] Emission images were obtained following intravenous injection of 18 mCi of cyclotron-produced nitrogen 13 (^{13}N) ammonia[36-43] or after 40 to 50 mCi of generator-produced rubidium 82, depending on availability of a generator (Bristol-Myers-Squibb, Princeton, NJ). The radionuclide used at baseline was also used in the final follow-up PET study.

At 5 to 10 minutes after the first dose of rubidium 82 or at 40 minutes after administration of the first dose of ammonia to allow for decay of the first radionuclide dose, dipyridamole (0.142 mg/kg per minute) was infused intravenously for 4 minutes. Two minutes after the infusion was complete, 25% of predetermined maximal handgrip was held by the patient with one hand for 4 minutes. Two minutes after the start of the handgrip, a second dose of the same amount of the same radionuclide was injected intravenously, with the handgrip continued for 2 minutes. The PET imaging was then repeated by the same protocol as for the resting study.

Transmission scans contained 100 million to 150 million counts. Emission scans of the whole heart contained 20 million to 40 million counts for 15 to 20 mCi of

intravenous ^{13}N ammonia and 15 million to 25 million counts for 40 to 50 mCi of rubidium 82.

Baseline and final dipyridamole images were displayed together for direct side-by-side comparison and were visually interpreted by three independent readers blinded to patient identification, quantitative data, treatment group, and all clinical information. The image pairs were randomized and were independently read by the three blinded readers as worse, better, unchanged, or showing mixed changes for different directional changes in the four quadrants and apex as described below. The visual change from baseline to final PET image was scored as no change, zero, or improved on a scale of +1, corresponding to definite but mild improvement, to +3 for maximal improvement, or –1 for definite but mild worsening to –3 for maximal worsening. A ±1 change corresponded to a one-color difference (eg, red vs yellow, representing a step in count density of 15% of maximum) between baseline and final PET scans; a ±2 change corresponded to a two-color difference (eg, red vs green); and a ±3 change corresponded to a three-color difference (eg, red vs blue) for a color scale as shown in Figure 1. Any change of +1 or greater was considered improved. Any change of –1 or less was considered worse. Any study with a change in one part of the heart of +1 or greater and a change in another part of –1 or less was considered to be a mixed change.

All measurements of severity and size of perfusion defects were carried out by computer analysis as previously described[16,25,38-40] without operator interpretation, visual drawing of borders, visual location of defect, or any other operator interaction, background subtraction, image enhancement, or other image manipulation. A three-dimensional restructuring algorithm generated true short- and long-axis views from PET transaxial cardiac images and three-dimensional views of the left ventricle as viewed from the right (septal), anterior, left lateral, and inferior views, reflecting relative regional activity distribution at rest and after dipyridamole stress. Polar maps and three-dimensional views are divided into fixed sections consisting of septal, anterior, lateral, and inferior quadrants and an apical segment of the polar or three-dimensional display.[16,25,38-40] The baseline PET scan was compared with the final PET scan by automated analysis of differences in size and severity of perfusion abnormalities, also without operator judgment, selection of areas of interest, or image manipulation.
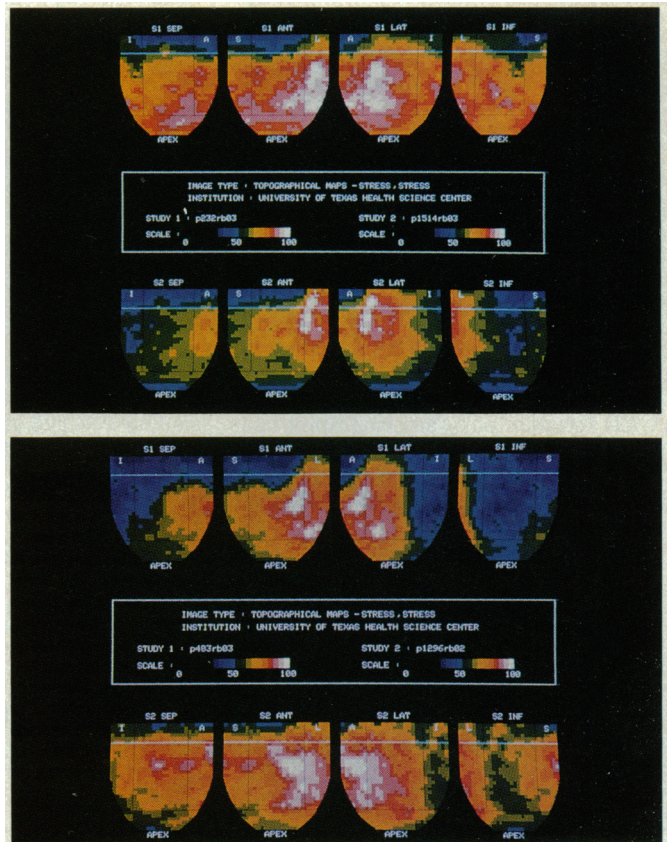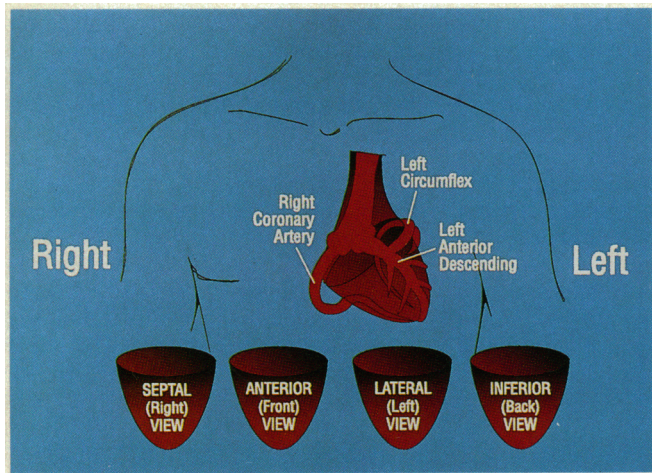
Figure 1.—Top left, Orientation of three-dimensional positron emission tomography (PET) images. Top right, Example of PET after dipyridamole at baseline (upper row) and after 5 years as a control patient (lower row) in right (septal), anterior, left lateral, and inferior views. Relative radionuclide uptake is shown in a graded-color scale ranging from maximum activity (100%) in white downward in 5% increments corresponding to the stepped color scale through red, yellow, green, blue, and black as minimum activity, shown in the color bars. The final study (lower row) compared with baseline (upper row) shows worsening throughout the heart, particularly inferiorly, corresponding to progression of three-vessel disease by quantitative coronary arteriography. Bottom right, Example of PET after dipyridamole at baseline (upper row) and after 5 years of lifestyle change (lower row) with the same views and color scale. The inferior perfusion defect becomes less severe with better, more uniform perfusion in the defect and in the rest of the heart corresponding to regression of three-vessel disease by quantitative coronary arteriography.

The end points were the severity and size of perfusion defects on PET images at rest and after dipyridamole stress, defined as follows: The end point *lowest quadrant average* was the average number of normalized counts for the quadrant having the lowest average activity, in which an anterior, septal, lateral, and inferior quadrant surround a central apex area. The mean value for any given quadrant with the lowest or minimum activity was the quadrant that contained the most severe perfusion defect. This lowest quadrant average was determined for the PET image at rest after dipyridamole stress. This end point quantified the relative severity of the perfusion abnormality. For example, a value of 65% would indicate that the mean count value for the quadrant with the lowest counts, and therefore containing the perfusion defect, would be 65% of the normal maximum of 100%.

The end point *percentage outside 2.5 SDs* was the size of the perfusion defect determined as the percentage of the cardiac image outside 2.5 SDs of that of normal individuals (based on 20 disease-free persons) for the PET image at rest or after dipyridamole stress. Because 2.5 SDs includes 97.6% of the normal distribution, there was only a 2.4% chance that normal values outside 2.5

SDs would be observed.

The end point *percentage with a ratio less than 0.6* was a measure of combined severity and size of perfusion abnormalities determined as percentage of myocardium with activity of less than 60% of maximum activity (100%) on the PET image. This measurement gives the size of the defect characterized by the severity threshold of less than 60% of the normal maximum of 100%, and therefore reflects the combined intensity and size of the defect on the PET image. A value of less than 0.6 or less than 60% of maximum on the PET image is approximately 3 SDs below the normal mean of $80\% \pm 7\%$ of maximum activity. Because 3 SDs contain 99.7% of the normal distribution, there was less than a 0.3% chance that normal values would be observed below 60% of maximum activity.

Statistical Analysis

Changes in perfusion abnormalities from the baseline to the final PET were compared between experimental and control groups by unpaired, one-tailed t test for continuous variables.[45-48] Data are reported as mean±1 SEM unless otherwise noted, reflecting the variability of means in each group and calculated as the SD divided by the square root of n, where n is the sample size of

the group. A one-tailed t test was justified on the grounds that improved lifestyle changes would not be expected to make perfusion abnormalities worse, as specified at the beginning of the study. Two-tailed t tests are also reported as more rigorous tests of significance. Analysis of variance was carried out using the Bonferroni post hoc correction algorithm[45-48] in Statview software (Abacus Concepts Inc, Berkeley, Calif). For discrete variables such as number or percentage of subjects showing changes greater than 1 SD from baseline values, significance of differences between groups was determined by Fisher's exact test (one tailed).[45-48]

Sample size was determined in initial trial design by power calculations from estimated changes expected and variability of quantitative arteriographic end points, the primary end points as previously reported for 1-year follow-up.[1,4] In view of previous reports on changes in arteriographic stenosis severity in this[1,4] and other trials,[1-24] we report arteriographic changes only briefly in comparison to PET results.

At entry into the study, four patients had one or more completely occluded coronary arteries with extensive collaterals to viable myocardium. These patients demonstrated severe perfusion ab-

Table 1.—Changes in Risk Factors*

Risk Factor	Experimental Group			Control Group			P†
	Baseline	5-y Follow-up	Change	Baseline	5-y Follow-up	Change	
Systolic blood pressure, mm Hg	135±15	128±14‡	−7±13	137±27	127±13	−11±21	.69
Diastolic blood pressure, mm Hg	82±9	77±8‡	−5±9	81±14	75±7	−5±13	.78
Weight, kg	91±15	83±12§	−8±6	76±18	78±19	+2±5	<.001
Cholesterol, mmol/L (mg/dL)	5.80±1.35 (225±53)	4.50±0.85 (175±33)§	−1.30±0.95 (−50±37)	6.45±0.95 (250±37)	5.95±0.85 (230±33)	−0.50±1.10 (−20±43)	.04
LDL cholesterol, mmol/L (mg/dL)	3.70±1.30 (143±50)	2.65±0.90 (103±35)§	−1.05±1.03 (−41±40)	4.35±0.78 (168±29)	3.80±0.90 (148±35)	−0.50±1.00 (−19±38)	.13
HDL cholesterol, mmol/L (mg/dL)	1.05±0.30 (40±12)	0.90±0.30 (35±11)	−0.15±0.35 (−5±13)	1.35±0.55 (53±22)	1.30±0.40 (50±16)	−0.03±0.40 (−1±15)	.26
Triglycerides, mmol/L (mg/dL)	2.58±1.34 (228±119)	2.78±1.20 (247±107)	+0.22±0.98 (+19±87)	2.62±2.84 (232±251)	2.20±0.76 (194±67)	−0.42±2.82 (−38±250)	.35
Adherence‖	0.67±0.37	1.14±0.24§	+0.55±0.29	0.60±0.29	0.71±0.27	+0.09±0.19	<.001

*LDL indicates low-density lipoprotein; and HDL, high-density lipoprotein. Numbers indicate mean±1 SD unless otherwise indicated.
†P for change, experimental group vs control group.
‡For baseline vs experimental period, P=.03.
§For baseline vs experimental period, P<.001.
‖See text for explanation.

normalities and myocardial steal after dipyridamole stress by PET. Myocardial steal by PET after dipyridamole stress is diagnostic for substantial coronary collateralization as compared with coronary arteriography.[41] Areas of myocardium showing myocardial steal would not be expected to show decreased size or severity of perfusion abnormalities corresponding to stenosis regression because the artery is occluded and usually does not reopen with lipid lowering. Myocardial steal and severity of perfusion defect after dipyridamole stress increase with time as resting collateral supply improves to myocardium distal to the occlusion.[49] Accordingly, image data were analyzed both with and without the four patients with myocardial steal.

RESULTS

Of the 48 patients enrolled, five (25%) of 20 patients in the control group and eight (29%) of 28 patients in the experimental group dropped out or were unavailable for follow-up study, including one control patient with bypass surgery, leaving 35 patients for analysis. Fifteen patients (12 men and three women) were in the control group and 20 patients (all men) were in the experimental group. Mean age of the experimental group was 57±6 years and of the control group 62±8 years.

Time from baseline control PET to the final PET study was 5.0±0.2 years (mean±1 SEM) and was comparable for control and experimental groups (5.1±0.2 years vs 4.9±0.2 years, respectively). Baseline characteristics of the control and experimental study groups were comparable, as previously reported.[1]

Differences between the control and experimental groups in the change from baseline to average values during the follow-up period for blood pressure, weight, serum cholesterol level, and adherence to the exercise, diet, and stress

management program are shown in Table 1. At final follow-up there was no difference in frequency, duration, or severity of angina pectoris between experimental and control groups, most likely due to revascularization procedures performed in the control group. Twenty patients (57%) were studied with ^{13}N ammonia at baseline and final PET studies, and 15 patients (43%) were studied with rubidium 82 at baseline and final PET studies, with the same proportion in the experimental and control groups. No systematic differences in the changes from baseline to final study were observed between these two perfusion radiotracers in the experimental vs the control group.

Figure 1, top right, shows the perfusion images in a control patient after dipyridamole at baseline (upper row) and at final follow-up 5 years later (lower row). In this control patient, the final study in comparison to baseline shows a marked decrease of activity in the inferior myocardium and a definite but less severe decrease in lateral, septal, anterior, and apical myocardium, reflecting decreased perfusion capacity corresponding to progression of three-vessel disease documented by quantitative coronary arteriography. From a patient in the experimental group (bottom right) the final study in comparison to baseline shows increased activity, particularly in the inferior myocardium but also in lateral, septal, anterior, and apical myocardium, reflecting increased flow capacity and regression of three-vessel disease by quantitative coronary arteriography. These examples illustrate characteristic changes that occurred in most patients.

Figure 2 shows the change in severity of myocardial perfusion abnormalities after dipyridamole stress measured as the lowest quadrant activity expressed as a percentage of maximum activity in

the heart. The quadrant with the lowest activity contains the most severe perfusion abnormality of the PET image after dipyridamole stress. In the control group, this lowest activity decreased further, indicating a more severe or worsening abnormality on the final study compared with the baseline study. In the experimental group, the lowest quadrant activity increased, ie, became less severe, indicating improvement in the perfusion abnormality on the final study compared with the baseline study. The differences in changes between control and treated groups were significant (P=.001 for a one-tailed t test; P=.002 for a two-tailed t test; and a power of 95%).

Figure 3 shows the change in size of myocardial perfusion abnormalities after dipyridamole stress expressed as percentage of the left ventricle (LV) outside 2.5 SDs of normal individuals. In the control group, the size of the myocardial perfusion defects increased, indicating a larger perfusion abnormality. In the experimental group, the size of the perfusion abnormalities decreased, indicating improvement. The difference in the changes between control and treated groups was significant (P=.02 for a one-tailed t test; P=.05 for a two-tailed t test; and a power of 70%).

Figure 4 shows the change in combined size and severity end point expressed as percentage of the LV with activity less than 60% of maximum activity. In control patients, the percentage of the LV below 60% of maximum activity increased, indicating worsening of the perfusion abnormality. In the experimental group, the percentage of the LV below 60% of maximum activity became smaller, indicating improvement in the perfusion abnormality. The difference in the changes between the control and experimental groups was significant (P=.002 for a one-tailed t test;
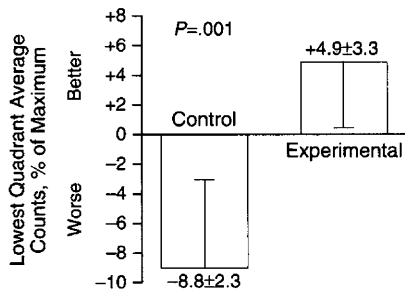
Figure 2.—Changes in severity of myocardial perfusion abnormalities by positron emission tomography after dipyridamole stress. Severity is measured as the lowest quadrant (as shown in Figure 1) average activity expressed as percentage of maximum activity. A decrease in activity, shown by a minus sign, indicates worsening; an increase in activity, shown by a plus sign, indicates improvement. The values shown are mean±SEM, with n=16 for the experimental and n=15 for the control group.
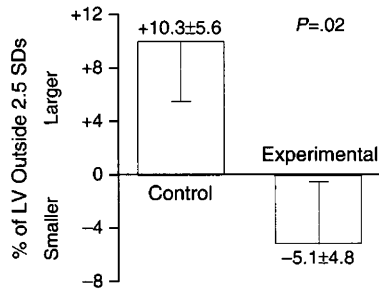

Figure 3.—Changes in size of myocardial perfusion abnormalities by positron emission tomography after dipyridamole stress. Size is measured as the percentage of the left ventricle (LV) outside 2.5 SDs of the normal range. An increase in size, shown by a plus sign, indicates worsening; and a decrease in size, indicated by a minus sign, indicates improvement. The values shown are mean±SEM, with n=16 for the experimental and n=15 for the control group.
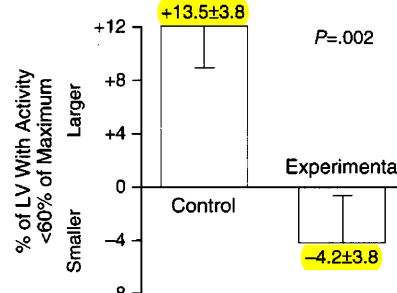

Figure 4.—Changes in combined size and severity of myocardial perfusion abnormalities by positron emission tomography after dipyridamole stress. The combined measure of size and severity is expressed as the percentage of the left ventricle (LV) with activity less than 60% of maximum, which is 3 SDs below the normal mean of 80%. An increase in size and severity is shown by a plus sign indicating worsening. A decrease in size and severity is shown by a minus sign indicating improvement. The values shown are mean±SEM, with n=16 for the experimental and n=15 for the control group.

$P=.004$ for a two-tailed t test; and power of 95%).

Table 2 shows the changes in three PET end points, including the four patients who, at entry, had occluded collateralized coronary arteries and myocardial steal after dipyridamole stress. The values for the experimental group (n=20) and the P values compared with those for the controls (n=15) in Table 2 are somewhat different than in Figures 2 through 4. The differences in changes between the control group and the experimental group (Table 2) remain statistically significant, although they were not as large due to unimproved size and severity of perfusion defects associated with myocardial steal in the four patients with occluded arteries at study entry. For Table 2, P values are for one-tailed t test, with the same results with two-tailed t testing.

Figure 5 shows the percentage of patients with significant changes, either worse or better, in size and/or severity of myocardial perfusion abnormalities after dipyridamole stress. Significant change in each of the three PET measurements of size and/or severity of perfusion abnormalities was defined as a change in each PET measurement on the final PET study that was greater than 1 SD of each PET measurement on the baseline studies of the control and experimental groups combined. The percentage of patients showing a threshold change defined in this way was averaged for each of the three PET measurements, and the resulting percentage of patients is shown in Figure 5. This analysis of patients based on a threshold change shows that 45% of controls had worsening defects, 50% showed no change, and 5% showed improvement. By comparison, most of the patients in

the experimental group showed improvement or no change. The difference in these changes between the control and experimental groups was significant ($P=.03$ by Fisher's exact test).

As a secondary end point, PET images were also visually interpreted independent of the automated quantitative analysis. Among three blinded readers there was agreement in 33 of 35 patients on whether the baseline to final dipyridamole images showed visual worsening, improvement, or mixed changes. In the two patients requiring consensus readings, all three readers agreed that these two patients showed mixed changes.

Visual interpretation of worsening or improvement did not agree with automated measurements indicating worsening or improvement in three patients who had mixed changes that the automated method determined as a net total change of improvement in one patient and worsening in two, a quantitative result not possible by visual interpretation. In 31 of the 32 remaining patients, the automated measurements concurred with visual interpretation of worsening or improvement. In the one case of disagreement between automated and visual analysis, the visual interpretation was borderline improvement, whereas the automated measurements showed borderline worsening.

Analysis of variance with the Bonferroni post hoc correction algorithm did not change these conclusions; P values for differences between the control and experimental groups for changes in size and severity of perfusion abnormalities by PET after dipyridamole were as follows: for lowest quadrant average counts, $P=.006$; for percentage outside 2.5 SD limits, $P=.04$; for percentage with

activity less than 60% of maximum activity on the dipyridamole image, $P=.01$.

Myocardial perfusion abnormalities by PET at resting conditions prior to dipyridamole stress also improved but not to the same degree as after dipyridamole because resting myocardial perfusion is less affected by coronary artery stenoses than is maximum perfusion capacity after pharmacologic arteriolar vasodilation.[25-32] The changes in size and severity of perfusion abnormalities on resting PET images were improved or better in the experimental group as compared with controls, with P values as follows: for the myocardial quadrant with the lowest average activity, $P=.02$ by one-tailed t test and $P=.04$ by two-tailed t test; for percentage of LV activity with less than 60% of the maximum activity on the resting PET image, $P=.01$ by one-tailed t test and $P=.02$ by two-tailed t test; for percentage of LV outside 2.5 SDs of normalized counts, $P=.06$ by one-tailed t test and $P=.11$ by two-tailed t test.

Figure 6 compares the changes in these three primary PET measurements with the changes in minimum lumen diameter, percent diameter stenosis, and stenosis flow reserve documented by quantitative coronary arteriographic analysis. Since the units of these six arteriographic and PET measurements are different, the absolute difference in changes between the control and experimental groups was expressed as a percentage of the mean of each measurement at baseline for all patients without the minus or plus sign for direction of change. For quantitative coronary arteriography, the difference in changes between the control and ex-

Table 2.—Changes in Perfusion Abnormalities by Positron Emission Tomography (PET)*

PET End Point	Control Group	Experimental Group	P
Lowest quadrant average counts, % of maximum	−8.8±2.3	+1.6±3.1	.008
% of LV outside 2.5 SDs	+10.3±5.6	−1.9±4.2	.04
% of LV with activity <60% of maximum	+13.5±3.8	−1.4±3.7	.004

*Final PET−baseline PET. Includes patients with total coronary artery occlusions at entry. LV indicates left ventricle. Numbers are mean±SD unless otherwise indicated.
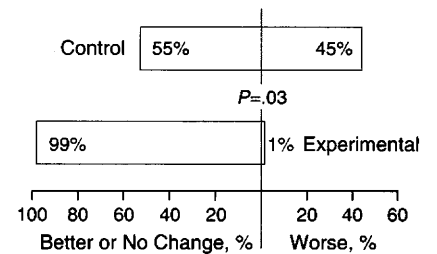

Figure 5.—Percentage of patients with significant changes greater than a threshold change, as defined below, in size and severity of myocardial perfusion abnormalities by positron emission tomography (PET) after dipyridamole stress. Significant change in each of the three PET measurements of size and severity of perfusion abnormalities was defined as a change in each PET measurement on the final PET study that was greater than 1 SD of each of the PET measurements on the baseline studies of the control (n=15) and experimental (n=16) groups combined. Values of each of the three PET end points for each patient were averaged separately for the experimental and control groups.

perimental groups ranged from 18% to 31% of the mean baseline value. For PET the difference in changes between control and experimental groups ranged from 22% to 96% of the mean baseline value.

COMMENT

This study demonstrates that the size and severity of myocardial perfusion abnormalities documented by PET at rest and after dipyridamole stress decrease or improve in patients undergoing intense risk factor modification in comparison to an increase or worsening in perfusion abnormalities in patients treated with standard therapy.

Although it is used as a measure of changing stenosis severity in lipid-lowering trials, percent diameter narrowing or absolute lumen size documented by coronary arteriography does not account for complex shape changes of stenoses.[4] Percent stenosis is also poorly related to flow capacity or coronary flow reserve[25-32] and fails to account for diffuse disease present in most patients with localized coronary artery narrowing.[33-35] The degree of improvement in percent stenosis in regression trials is quite modest, ranging up to 5% diameter stenosis units for all stenoses and up to 10% of diameter stenosis for more severe stenoses.[1-24,50,51] These modest anatomic changes reported in recent cholesterol-lowering trials raise questions about their functional significance. In this study, the substantial improvement in perfusion abnormalities measured by PET images documents the functional significance of relatively small changes in the atherosclerotic coronary arterial circulation associated with this modest extent of arteriographic regression in long-term cholesterol-lowering trials.

The improvement in size and severity of myocardial perfusion abnormalities at resting conditions and after dipyridamole stress in comparison to worsening in controls most likely involves two mechanisms. The first is partial anatomic regression of localized coronary artery stenosis as demonstrated by quantitative coronary arteriography, which improves maximum flow capacity and decreases size and severity of perfusion abnormalities after dipyridamole stress. A second mechanism for decreased size

and severity of perfusion abnormalities by dipyridamole-PET may be improved endothelial-mediated coronary artery and arteriolar vasomotor function occurring within weeks to months after vigorous cholesterol lowering but before anatomic regression occurs.[16]

Both coronary atherosclerosis and hypercholesterolemia impair endothelial-mediated vasodilation of epicardial coronary conduit arteries.[52-68] Dietary fat restriction, lipid reduction by drugs, or both restore this endothelial-mediated epicardial artery vasodilation in experimental animals[53,56,59,62] before anatomic regression of CAD is seen.[69] Changes in the coronary microcirculation may play a role in the observed improvement in perfusion defects. Atherosclerosis of proximal, conduit, and epicardial coronary arteries impairs endothelial-mediated vasodilation of the distal microcirculation.[54,55,59,62,64] Therefore, the coronary flow response induced by the direct effect of dipyridamole on arteriolar vasodilation may be augmented by an improved flow-mediated, endothelial-dependent, further arteriolar vasodilation in response to the initial increased flow induced by the effect of dipyridamole.

Since coronary artery stenoses affect maximum flow capacity much more than resting flow, the improvement in resting perfusion abnormalities suggests diffuse improvement in vasomotor function throughout the coronary arterial and arteriolar circulation in the experimental group compared with controls.

These results also provide a mechanism explaining the substantial decrease in angina pectoris reported to occur early in lipid-lowering trials.[1-23] Because myocardial perfusion reflects the integrated effects of single or multiple stenoses, diffuse atherosclerosis, and vasomotor dysfunction on coronary flow, quantitative PET perfusion imaging provides information on severity of CAD beyond a single dimension of a single localized coronary artery narrowing as measured on an arteriogram. Furthermore, because perfusion is related to lumen radius raised to the fourth power,[25-29] small changes in arteriographic lumen diameter that are difficult to measure on the arteriogram produce proportionately greater changes in perfusion that are apparent on PET scan.

Using end point measurements of stenosis severity, arteriographic regression trials have compared average change in stenosis severity between control and experimental groups or have compared the percentage of patients showing a change in severity greater than some threshold value, reflecting inherent variability of the measurement technique. In this study we analyzed the PET data using both of these approaches and found concurring results.

Lipid-lowering trials have also characteristically categorized patients or stenoses as showing regression or no change as opposed to progression in severity. The reason is that progression is associated with high risk of future coronary events, such as death, myocardial infarction, bypass surgery, or balloon angioplasty, whereas partial regression or stability of coronary artery stenoses is associated with low risk of coronary events.[2,15,50,70] Accordingly, in our analysis based on threshold change in the PET images (Figure 5), we categorized patients as showing improvement or no change vs progression in size and severity of perfusion abnormalities due to these observed prognostic implications.

In view of several previous trials demonstrating modest arteriographic regression of single, localized coronary artery stenoses, the current study reports unique, long-term follow-up data on the functional and mechanistic correlates of these arteriographic changes seen after a variety of lipid-lowering interventions. The greater changes in size and severity of perfusion abnormalities obtained noninvasively in this study may be interpreted as being functional consequences of or correlates with the mod-
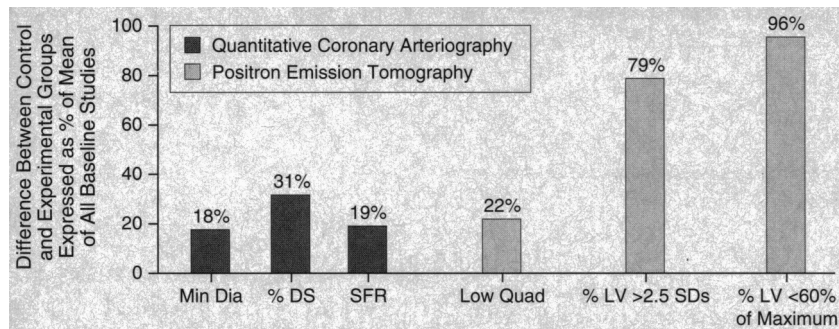
Figure 6.—Comparison of changes by positron emission tomography (PET) and quantitative coronary arteriography (QCA). The PET measures were myocardial quadrant with the lowest average activity (Low Quad), percentage of left ventricle (LV) outside 2 SDs of normals, and percentage of LV activity less than 60% of maximal activity. Measurements by QCA were minimum absolute lumen diameter (Min Dia); percent diameter stenosis (% DS) and stenosis flow reserve (SFR) derived from the integrated effects of absolute lumen diameter, % DS, and cumulative length effects based on fluid dynamic equations, all as previously validated and reported.[2-7] The absolute difference in changes between the control and experimental groups (without the minus or plus sign for direction of change) was expressed as a percentage of the mean of each measurement at baseline for all patients.

est anatomic changes in stenosis severity measured by invasive arteriography.

The principal limitation of the current study is the relatively small number of subjects. However, differences in PET images between control and experimental groups were statistically significant. During the 5-year follow-up period of this study, five (25%) of 20 control patients and eight (29%) of 28 patients in the experimental group dropped out of the study or were unavailable for follow-up, or data were lost by computer malfunction. The dropout rate averaged 5% per year, comparable to that in other trials, and was comparable in control and experimental groups without identifiable bias in the results. While some unrecognized bias from dropouts, small sample size, or patient selection might limit the generalizability of the effects of the lifestyle intervention, it would not be expected to affect results of size and severity of perfusion abnormalities by PET. Noninvasive functional measures of disease severity were comparable to or, in some respects, better than invasive coronary arteriography performed in the same patients.

The total cost of diagnosis and follow-up by noninvasive PET at $2200 per study for all component costs is comparable to typical total costs of $2500 for single-photon emission computed tomography (SPECT) stress perfusion imaging and is less than $8000 to $10 000 for all costs of coronary arteriography.[71] This study focused on changes in myocardial perfusion using the most quantitative, accurate imaging currently available, which PET provides due to attenuation correction and uniform, depth-independent high resolution. Pharmacologic stress is also readily standardized despite changing maximal exercise work-

load due to changing anginal thresholds that alter the vasodilatory stimulus at follow-up studies compared with baseline. Whether changes in myocardial perfusion can be reliably followed up by SPECT, exercise stress, or both is unclear. Eight recent studies of a total of 4064 cases suggest that attenuation artifacts limit the accuracy of SPECT[72] and reduce its reported sensitivity and specificity to 86% and 54%, respectively, compared with 95% and 95% for PET based on 855 cases in nine reports.[71] In view of technical limitations, further randomized studies would be necessary to document the validity of SPECT for this application in comparison with coronary arteriography.

In conclusion, the modest regression of coronary artery stenosis in patients with coronary atherosclerosis after intense risk factor modification is associated with significantly decreased size and severity of perfusion abnormalities by rest-dipyridamole PET perfusion imaging as compared with worsening of perfusion in control patients treated with standard antianginal therapy at 5-year follow-up. Progression or regression of CAD can be followed up noninvasively by objective automated quantitation or qualitative visual interpretation of perfusion abnormalities by rest-dipyridamole PET perfusion imaging.

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