Clinical Investigation and Reports

Short-term Cholesterol Lowering Decreases Size and Severity of Perfusion Abnormalities by Positron Emission Tomography After Dipyridamole in Patients With Coronary Artery Disease

A Potential Noninvasive Marker of Healing Coronary Endothelium

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Background Cholesterol lowering over 1- to 3-year trials is associated with modest regression or no progression of focal coronary artery stenoses compared with progression in controls, a decrease in cardiac events proportionately more than the modest improvement in percent stenosis, and in experimental animals improved endothelial-mediated coronary vasodilation.

Methods and Results Accordingly, we hypothesized that there would be improvement in size and severity of perfusion abnormalities by rest-dipyridamole positron emission tomography (PET) imaging in a randomized intensive cholesterollowering trial with each patient studied after a baseline control period, a 90-day intensive cholesterollowering treatment, and a final control period off cholesterollowering regimens. Completely automated, objective measures of size and severity of perfusion abnormalities on rest-dipyridamole PET images were made by computer algorithm in 12 patients with coronary artery disease. There were statistically significant decreases (improvement) in size and severity of perfusion abnormalities by rest-dipyridamole PET on comparison of baseline control with perfusion abnormalities after intensive 90-day cholesterollowering and significant increases (worsening) in size and severity after the final control period, respectively, as follows. (1) The percent of left ventricle outside 2.5 SD of normal values on the dipyridamole-to-rest ratio image of normalized counts was 22±20% after the initial control period, 13±14% after the treatment period, and 26±22% after the final control period with a significant decrease (improvement) occurring between the initial control and treatment periods (P=.02) and an increase (worsening) occurring between the treatment and final control periods (P=.009). (2) The percent of left ventricle with a ratio of ≥0.66 in the dipyridamole-to-rest ratio image of normalized counts was 11±13% after the initial control period, 5.8±10% after the treatment period, and 14±19% after the final control period with a significant decrease (improvement) occurring between the initial control and treatment periods (P=.04) and an increase (worsening) occurring between the treatment and final control periods (P=.02). (3) The myocardial quadrant on the polar display with the lowest average activity expressed as a percent of maximal activity was 0.81±0.18 after the initial control period, 0.87±0.014 after the treatment period, and 0.77±0.23 after the final control period with significant improvement occurring between the initial control and treatment periods (P=.05) and worsening occurring between the treatment and final control periods (P=.05).

Conclusions These results suggest that relatively short-term, intensive cholesterollowering over 90 days improves myocardial perfusion capacity before anatomic regression of stenoses occurs and that such improvement, or deterioration after withdrawal of lipid-lowering treatment, can be followed noninvasively by dipyridamole PET, reflecting the integrated flow capacity of the entire coronary arterial/arteriolar vascular system affected by diffuse atherosclerosis. (Circulation. 1994;89:1530-1538.)

Key Words • cholesterol • tomography • perfusion • imaging • dipyridamole • coronary artery disease

Several randomized arteriographic trials have demonstrated that reducing serum cholesterol by diet and/or cholesterollowering drugs over a period of 1 or more years is associated with modest but statistically significant partial regression or no progression of coronary artery stenosis compared with progression in controls.1-10 There also is a substantial decrease in clinical cardiac events in treated groups compared with controls that is proportionately larger than expected in comparison to the modest but significant improvement in anatomic stenosis severity.5,8,11-13

In experimental animals13-25 and in humans,26-28 coronary artery disease and/or hypercholesterolemia impairs coronary arterial and distal arteriolar vasodilation

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mediated by endothelium. In experimental animals, lowering serum cholesterol or treatment with fish oil improves this endothelial-mediated vasodilatory capacity of coronary arteries and/or arterioles in relatively short time periods. Quantitation of focal stenoses on coronary arteriograms does not account for the cumulative effects of diffuse coronary atherosclerosis or the perfusion capacity of the integrated coronary arterial arteriolar vascular system. Accordingly, in a randomized, control-treatment-control sequential study design, we tested the hypothesis that in patients with coronary artery disease, marked cholesterol lowering over a relatively short time period of 90 days would reduce the size and severity of perfusion abnormalities imaged by positron emission tomography (PET) after intravenous dipyridamole, thereby indicating improved perfusion within a relatively short time period before anatomic regression of coronary artery stenosis occurs. As a corollary control measurement, we hypothesized that a second control period after withdrawal of lipid-lowering treatment would result in increased size and severity of PET perfusion abnormalities that would become comparable to the initial baseline control, thereby documenting the functional nature of the changes rather than anatomic regression.

Methods

**Patient Selection**

For inclusion in the study, either men or women over 30 years old had to have all of the following: coronary artery disease with 50% or more diameter stenosis in one or more major epicardial coronary arteries documented by coronary arteriography, stable angor pectoris, positive exercise tolerance test, serum cholesterol of 250 mg/dL and serum triglycerides of less than 200 mg/dL. Women over 30 years with no other risk factors for CAD were also eligible if they had no history of heart disease, diabetes, or hypertension. Patients with unstable angina pectoris, transient ischemic attacks, primary nonischemic cardiomyopathy, uncontrolled congestive heart failure, ventricular arrhythmia, and progression of coronary disease were not included in the study. Concurrent treatment with antihypertensive medications, including calcium channel blockers, was allowed.

**Study Design**

The purpose of the study was to determine the short-term effects of marked cholesterol lowering on perfusion abnormalities by PET after dipyridamole using a controlled, randomized, control-treatment-control design with the smallest possible number of patients where each patient during treatment was compared with himself or herself during a pretreatment control period off lipid-lowering regimens, during intensive cholesterol-lowering treatment, and during a final control period off the lipid-lowering regimen. A particular strength of the control-treatment-control sequence was to evaluate worsening of perfusion abnormalities after withdrawal of cholesterol-lowering treatment that likely would not be associated with anatomic regression and progression over such a short time course.

The study design called for 60 patients to be randomized to one of three treatment groups outlined below at four different sites in four different states. Sequential patient numbers 1 through 60 were randomly assigned to one of the three treatment groups by the Statistical Analysis Division of Baxter Health Care Corporation using SAS software, which generates random numbers for randomization in blocks of three patients corresponding to the three treatment groups (SAS Institute, Inc). Change in size and severity of perfusion abnormalities by rest-dipyridamole PET was the primary end point as described below. However, after 15 patients were recruited and randomized, funding support was terminated for business reasons. No patients with complete data were recruited at other sites. The completely agreed to treat the patients randomized into each treatment group with the short-term, intensive cholesterol lowering on perfusion abnormalities by dipyridamole PET regardless of how it was achieved. Therefore, it was important to demonstrate the effects of marked cholesterol lowering by several different treatment regimens to emphasize cholesterol lowering per se rather than a specific clinical regimen or a direct effect of cholesterol-lowering drugs independent of cholesterol changes. Accordingly, patients were randomly assigned as described above for a 90-day period to one of the three following cholesterol-lowering protocols.

First, the current practice (group C) group consisted of a National Cholesterol Education Program (NCEP) Step 2 diet (30% of calories as fat with saturated fat less than 7% of calories and cholesterol less than 200 mg/dL, 10% to 20% as protein, and 50% to 60% as carbohydrate) with dietitian assistance, 20 mg Lovastatin BID, and 1 packet cholestyramine (Questran Light) BID.

Second, the no fat-enteral diet (group N) group consisted of an enteral protein supplement (a lactalbumin concentrate) comprising 25% to 30% of calories, carbohydrate supplements of maltodextrin, sucrose and fresh fruits and vegetables comprising 69% to 74% of calories, vitamins, minerals, electrolytes, and water. This diet had a fat content of less than 2% of total calories.

Last, the total parenteral nutrition (group T) group consisted of continuous 24-hour intravenous infusion of a lipid-free solution containing all essential nutrients without oral intake except water. Protein was provided as 1.5 to 1.7 g/kg body wt of amino acid (10.25% Atheromine, Baxter Healthcare Corp) in a sterile, nonpyrogenic, aqueous, hypertonic solution of essential and nonessential amino acids. Calories were provided as dextrose. Electrolytes, vitamins, and trace elements were added to the parenteral solution in a volume of 2500 ml to 3000 ml/24 h that was compounded in the pharmacy and delivered to the patient's home. This arm of the study required insertion of a central venous catheter under aseptic conditions by an experienced surgeon. Home monitoring was maintained by home care nurses trained in management of chronic indwelling catheters for parenteral nutrition. Each patient was his or her own control with a 3-week control period on an NCEP Step 2 diet without lipid-altering drugs before a 3-month treatment period in either group C (current practice), group N (no-fat enteral diet), or group T (total parenteral nutrition). At the end of the 90-day treatment period, each patient underwent a 60-day control period of "washout" on an NCEP Step 2 diet and off lipid-altering drugs. In view of seven randomized trials already published showing the benefits of cholesterol lowering by arteriography and major decreases in clinical events, study design was not intended at any time to address whether cholesterol lowering was associated with reversal or no progression of stenoses in treated compared with untreated controls. We therefore emphasize that the study design was intended to address the short-term effects of cholesterol lowering on PET perfusion defects after dipyridamole with each patient serving as his or her own control before and after the treatment period.
Standard antianginal cardiac medications were continued throughout the baseline control period, the 90-day treatment period, and the final control period off the lipid-lowering regimen. The treatment protocol included no stress management or exercise routines. Cardiac PET before and after dipryidamole and serum lipid profiles were obtained at the end of the first 3-month control period, at the end of the 3-month treatment period, and at the end of the 60-day control period. Patient selection, implementation of the cholesterol-lowering regimens, and clinical management were carried out independent of and without knowledge of or input from the investigator responsible for carrying out cardiac PET (K.L.G.), which was analyzed automatically by computer algorithms without operator judgment, drawing regions of interest or any other data manipulation, as detailed below.

This randomized assignment of patients to each of three markedly different cholesterol-lowering regimens and the control-treatment-control design provide optimal statistics for documenting the short-term effects of low fat intake and cholesterol lowering with the smallest number of patients, when each patient acts as his or her own control to evaluate the effects of marked cholesterol lowering generically regardless of how it is accomplished. The control-treatment-control design also provides information on following the worsening of perfusion abnormalities (treatment compared with second control) as well as improvement (first control compared with treatment), changes not likely explained by anatomic regression and progression of stenoses.

Fifteen patients were enrolled in the study at the Houston site where PET was available, with 1 patient in each group failing to complete treatment for the following reasons: 2 withdrew, and 1 had coronary artery bypass graft surgery. The remaining 12 patients form the basis of reported data. The final data set consisted of 3 patients assigned randomly to group C (current practice), 3 patients to group N (no-fat enteral diet), and 6 patients to group T (total parenteral nutrition). Although there are unequal numbers of patients in the three treatment groups, these numbers reflect the randomized assignment of the first 15 patients as described previously. Because the smaller pilot study was intended to document the effects of marked cholesterol lowering by any of several markedly different protocols, comparisons between groups were not of primary interest but rather comparisons were made of each patient during cholesterol lowering with himself or herself during the initial and final control periods. Although there were no significant differences in the results of perfusion imaging among the three treatment protocols, the sample sizes are too small for definitive comparisons of the different treatment groups.

Daily alimentation logs were maintained for each patient. Fasting blood samples were obtained weekly for complete chemistry analysis, lipid profiles, and amino acid profiles by Smith Kline Beecham Clinical Trial Center Laboratories, Van Nuys, Calif. The adequacy of essential fatty acids was monitored by measuring the triene-to-tetraene ratio (or ratio of fatty acid C20:3ω9 to fatty acid C20:4ω6). If the ratio of these two fatty acids is more than 0.4 in serum phospholipids, the patient may be considered to be deficient in essential fatty acids. In this study, no patient showed evidence of essential fatty acid deficiency. Average weight decreased from 178±20 to 172±16 lb at the end of the treatment period, a small but statistically significant decrease (P=0.02).

PET

PET imaging of myocardial perfusion at rest and after dipryidamole was carried out as previously described and is summarized briefly. Patients were fasted for 8 hours, and caffeine, theophylline, and cigarettes were withheld for 8 hours before the study. Fluoroscopy was used to mark the cardiac borders for patient positioning. Scans were performed using the University of Texas cesium fluoride multislice tomograph with a reconstructed resolution of 12-mm full width at half-maximum (FWHM) inplane and 14-mm FWHM axially. Transmission images were performed to correct for photon attenuation using the Segmented Attenuation Correction Method first reported by this laboratory. Emission images were obtained after intravenous injection of 18 mCi of cyclo-tron-produced [15N]ammonium, as previously described. Image acquisition was delayed for 3 minutes after ammonium administration to allow pulmonary and blood pool clearance. Data were acquired for 15 to 20 minutes for [15N]ammonia.

At 40 minutes after administration of the first dose of [15N]ammonia, dipryidamole (0.142 mg·kg⁻¹·min⁻¹) was infused for 4 minutes. Two minutes after the infusion was complete, 25% of predetermined maximal handgrip was held with one hand for 4 minutes. Two minutes after the handgrip was started, a second dose of the same amount of the same tracer was injected, and imaging was repeated. For those patients developing significant angina, aminophylline (125 mg) was given intravenously.

Transmission scans contained 100 to 150 million counts. Emission scans contained 20 to 40 million counts for 15 to 20 mCi of intravenous [15N]ammonia.

Three-dimensional Restructuring Algorithm of PET Scans

To obtain objective, quantitative measurements of changes in PET perfusion defects without observer bias in interpretation or selecting regions of interest, a completely automated analysis of size and severity of PET abnormalities was carried out using previously described software. Our three-dimensional restructuring algorithm for generating true short- and long-axis views from PET transaxial cardiac images has been validated by testing with computer-generated and phantom data sets with a <1% error in restructured short-axis images. Restructured short-axis views serve as input data to a routine that computes polar coordinate maps for rest and dipryidamole images. Alternatively, to avoid the visual spatial distortion inherent in polar displays, the circumferential profiles are used to reconstruct three-dimensional views of the left ventricle as viewed from the right (septal), anterior, left lateral, and inferior views, also previously described. A set of four specialized polar coordinate maps and three-dimensional displays reflecting regional activity distribution at rest and after dipryidamole stress, the change in absolute activity, and the change in relative rest-to-stress distribution were created using rest and stress circumferential profile data as input.

Quantitative Analysis of Regional Activity

To quantitate relative regional activity, all polar maps and three-dimensional views are divided into fixed sections representing the septal, anterior, lateral, inferior, and apical quadrants of the polar or three-dimensional display. The basal portion of the data, corresponding to the atroventricular ring or outer circumferential rim of the polar map, is excluded from the quantitative analysis because the basal portions of the polar maps contain more statistically deviant data than the other portions that adversely affect statistical analysis.

A minimal algorithm for each quadrant of each polar map and three-dimensional view determines the lowest average 5% of the data as the regional minimal activity value. The mean algorithm determines, for each of the polar maps and three-dimensional views, the mean activity level in each of the five regions. A fractionation routine provides the percent of the cardiac image with given relative activity levels for each of the specialized polar maps and three-dimensional views. To eliminate the geometric distortion inherent in polar displays, the circumferential profiles from true short-axis views that define the polar maps serve as input to the fractionation routine and are displayed as three-dimensional views without the marked spatial distortion inherent in polar map displays.
Finally, a pixel blackout routine automatically identifies regions for each polar map and three-dimensional view that has a value that deviates significantly from standard normal values based on studies of 20 disease-free individuals. The blackout algorithm creates standard deviation blackout polar maps by performing sector-by-sector comparisons of polar map images from an individual study with sets of normal standard deviation images of 1.5, 2.0, and 2.5 SD. The blackout routine then computes the percent of circumferential profile units that are blacked out in the anterior, lateral, septal, inferior, and apical regions of each of the standard deviation polar maps. Thus, the percent of the cardiac image that falls beyond 1.5, 2.0, or 2.5 SD from normal is automatically determined regionally and for the whole heart for each of the four specialized polar maps and three-dimensional views.

All measurements of severity and size of perfusion defects were carried out completely automatically by computer without operator intervention, visual drawing of borders, visual location of defect, or any other operator interaction. The sequence of PET scans resulted in two control studies and one treatment study between the initial and final control studies. Analysis was made of the three studies in sequence and of the two control studies compared with the treatment study.

**PET End Points**

The end points were the severity of perfusion defects and size of perfusion defects measured automatically by computer analysis of the PET images, defined as follows. The end point lowest quadrant average is the average number of counts for a quadrant, where there is an anterior, septal, lateral, and inferior quadrant surrounding a central apex area, which was also analyzed automatically. The mean value for any given quadrant that was the lowest or minimum was the quadrant that contained the perfusion defect. This lowest quadrant average was determined for the ratio image of dipyridamole to rest using normalized counts. For an idealized normal heart, the quadrant average on the ratio image of dipyridamole to rest using normalized counts would be 1.0, or 100%. A value of 80% would indicate that the mean count value for the quadrant with the lowest counts, and therefore containing the perfusion defect, would be 80% of the normal 100% expected. The end point percent outside 2.5 SD is the size of the perfusion defect determined as the percent of the cardiac image outside of 2.5 SD of normal for the ratio image of dipyridamole to rest using normalized counts. The end point percent with ratio of <0.66 is a second measure of size determined as percent of myocardium that had a ratio of less than 66% on the ratio image of dipyridamole to rest using normalized counts. This last size measurement gives the size of the defect characterized by the threshold ratio of less than 66% of maximum, with normal being 100%. It therefore reflects both the combined intensity and the size of defect on the PET image.

**Statistical Analysis**

Automated measures of perfusion abnormalities by PET after dipyridamole were compared for the 12 patients by paired t testing of the first control period with the treatment period and of the second control period with the treatment period (Tables 2 and 3), with each patient compared with his or her own control periods. Because the experimental design was not intended to look for differences among group C, group N, and group T, between-group comparisons were not of primary interest, but rather each patient after treatment was compared with himself or herself during the baseline and final control periods. Although there were no differences in PET results among the three treatment groups as shown below, sample sizes are too small for intergroup comparisons.

**Results**

Table 1 shows the changes in total serum cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Total cholesterol and LDL cholesterol fell significantly; HDL cholesterol and triglycerides fell but not significantly. Table 2 shows the changes in automatically determined size and severity of perfusion abnormalities from ratio images of dipyridamole to rest by PET. The size of the perfusion defect expressed as percent of the cardiac PET image outside of 2.5 SD of normal decreased from an average of 22% for first control period to 13% at the end of the 3-month cholesterol-lowering regimen and increased to 26% in the second control period. These differences between control and treatment periods were highly statistically significant.

A second end point combining the size of the perfusion abnormality with its severity was the percent of the ratio image of dipyridamole to rest using normalized counts that was less than 0.66, ie, the size of the defect with activity that was less than 66% of normal maxi-

| TABLE 1. Changes In Lipids and Lipid Subfractions |
|-----------------|-------------|--------|--------|---------|
| Sample          | Total Cholesterol | LDL    | HDL    | Triglycerides |
| Baseline control| 297±69       | 213±79 | 41±7   | 241±105  |
| End of treatment| 224±72       | 151±59 | 34±11  | 199±72   |
| Final control   | 299±69       | 207±67 | 42±8   | 240±98   |

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein. Values are mg/dL, mean±1 SD. *P<.01 for differences between control and treatment periods.

| TABLE 2. Ratio Image of Normalized Counts, Dipyridamole to Rest |
|-----------------|-------------|--------|--------|---------|
| Size and Severity of PET Defects | Control PET 1 | P  | Treatment PET 2 | P  | Control PET 3 |
| Percent outside 2.5 SD | 22±20% | .02 | 13±14% | .009 | 26±22% |
| Percent with ratio <0.66 | 11±13% | .04 | 5.8±10% | .02 | 14±19% |
| Lowest quadrant average | 0.81±0.18 | .05 | 0.87±0.14 | .05 | 0.77±0.23 |

PET indicates positron emission tomography.
mum. The size of the ratio image of dipyridamole to rest with less than 66% of normal maximal activity decreased from 11% for the first control period to 5.8% at the end of the 3-month treatment period and increased to 14% in the second control period. These differences between the control and each treatment periods were also highly statistically significant.

The severity of perfusion abnormalities on the PET image after dipyridamole was described by the automatically determined lowest average value of the four quadrants and apex, one or more of which contained the perfusion defect. This lowest quadrant average of normalized counts improved from 0.81 (1.0 being normal maximum) for the first control period to 0.87 at the end of the treatment period and fell to 0.77 in the final control period. The differences between the control and each treatment period were modest but statistically significant.

Because size and severity of perfusion abnormalities by PET were not different between the first and final control periods, quantitative values for these two control periods were averaged for each patient as a single control in comparison to the treatment period, as shown in Table 3. Both size and severity of perfusion abnormalities by PET after dipyridamole improved during the cholesterol-lowering period compared with averaged initial and final control periods with highly significant statistical differences.

Table 3. Ratio Image of Normalized Counts, Dipyridamole to Rest

<table>
<thead>
<tr>
<th>Size and Severity of PET Defects</th>
<th>Average Control</th>
<th>PET 1 and PET 3</th>
<th>Treatment</th>
<th>PET 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent outside 2.5 SD</td>
<td>23±17%</td>
<td>.0003</td>
<td>13±14%</td>
<td></td>
</tr>
<tr>
<td>Percent with ratio &lt;0.66</td>
<td>12±14%</td>
<td>.003</td>
<td>5.8±10%</td>
<td></td>
</tr>
<tr>
<td>Lowest quadrant average</td>
<td>0.80±0.17</td>
<td>.01</td>
<td>0.87±0.14</td>
<td></td>
</tr>
</tbody>
</table>

PET indicates positron emission tomography.

Fig 1 shows for each individual patient the average control and treatment values of the percent of the left ventricle with the ratio of dipyridamole to rest outside 2.5 SD of normal for the ratio image of dipyridamole to rest using normalized counts observed at the end of the 90-day treatment period compared with the average of the baseline and the final control periods. In individual patients, there was a consistent decrease in size of the dipyridamole perfusion abnormality during the lipid-lowering treatment period compared with initial and final control studies off lipid-lowering treatment.

There was no significant difference between the three treatment groups in changes on PET images. The average of first and final control values compared with the treatment period was as follows. For percent of left ventricle outside 2.5 SD, group C control was 14±16% or worse compared with treated (6±6%); group N control was 41±20% or worse compared with treated (27±23%) (P=.02); and group T control was 18±11% or worse compared with treated (7±5%) (P=.01). For percent of left ventricle with a ratio of dipyridamole to rest of less than 0.66, group C control was 8±11% or worse compared with treated (3±3%); group N control was 26±21% or worse compared with treated (16±17%) (P=.04); and group T control was 7±8% or worse compared with treated (2±2%) (P=.02). For lowest quadrant average, group C control was 0.87±0.19 or worse compared with treated (0.89±0.08); group N control was 0.63±0.23 or worse compared with treated (0.76±0.20); and group T control was 0.85±0.09 or worse compared with treated (0.92±0.12).

Fig 2A illustrates an example of the baseline, control rest PET (top row), and dipyridamole PET images (bottom row) in right (septal), anterior, left lateral, and inferior views (left to right, respectively) of a patient with a severe inferior resting defect that was larger and more severe after dipyridamole. Fig 2B illustrates the dipyridamole images at baseline control (top row) after the 3-month treatment period (middle row) and for the final control period (bottom row) showing a somewhat smaller, less severe inferior abnormality at the end of the 3-month treatment period compared with the larger, more severe abnormalities on baseline and final control images. Visually, perfusion appeared to be improved and more uniform throughout the heart, particularly in border zone areas of defects, thereby making them smaller.

Patients improved clinically after the treatment period, with duration on the modified Bruce protocol increasing from 10.7±3.5 to 13.3±3.9 minutes (P=.04) and frequency of angina decreasing by 51±25%.

Discussion

The present study shows that marked cholesterol lowering over 90 days in hyperlipidemic patients with coronary artery disease decreased the size and severity of the perfusion defects measured objectively and automatically by rest-dipyridamole PET imaging compared with the baseline control study; subsequently, the perfusion defects increased in size and severity in the final control washout period, becoming comparable to those in the initial control baseline study, with both being significantly larger and more severe than those after the treatment period. Recent cholesterol-lowering trials have demonstrated modest, statistically significant regression or no progression of the anatomic severity of stenoses after periods of 1 to 2 years of treatment. Our
results suggest that vigorous cholesterol lowering over a relatively short period improves myocardial perfusion capacity in patients with coronary artery disease.

The mechanisms for improved perfusion defects after 90 days of marked cholesterol lowering are unclear. Anatomic regression of stenoses is not a likely explanation of the sequential opposite changes occurring over a relatively short period in the same patient. Diverse methods for lowering cholesterol appear to have these effects, including an extremely low-fat diet, moderate low-fat diet plus cholesterol-lowering drugs, and total parenteral, fat-free alimentation. Although the numbers of patients in each sub-group were too small for definitive comparisons of the specific methods for lowering cholesterol, it appears unlikely that a direct effect of cholesterol-lowering drugs on endothelium or vascular smooth muscle is an explanation for the improvement in size and severity of perfusion abnormalities because this improvement was also observed in two groups not treated with cholesterol-lowering drugs.

Our results in humans are consistent with experimental studies in animals showing restoration of endothelium-dependent vasodilation by dietary fat restriction and/or lipid manipulation based on the following reasoning. Dipyridamole inhibits adenosine deaminase, thereby increasing the release of endogenous adenosine and effects of exogenous adenosine, which causes direct coronary arteriolar vasodilation mediated by an adenosine receptor on the arteriolar vascular smooth muscle cell. Like adenosine administered intravenously or intracoronary, the arteriolar vasodilation after dipyridamole is the result of a direct effect on coronary arteriolar smooth muscle and is not mediated by endothelium.

Both coronary atherosclerosis and hypercholesterolemia impair endothelial-mediated vasodilation of epicardial coronary conduit arteries, including large artery vasodilation normally occurring at high flows induced by distal arteriolar vasodilation. Dietary fat restriction and/or lipid manipulation restores endothelium-mediated epicardial artery vasodilation in experimental animals. In the presence of coronary artery atheromatous narrowing, either segmental or diffuse, loss of endothelial-mediated, epicardial artery vasodilation, or paradoxical vasconstriction that occurs, would make the severity of coronary artery narrowing worse with further impairment of flow capacity or maximal flow after direct arteriolar vasodilation by dipyridamole.

Accordingly, we hypothesize that the mechanism for decreased size and severity of perfusion abnormalities by dipyridamole PET during the cholesterol-lowering period is the result of improved endothelial-mediated, epicardial artery vasodilation in response to high flows after direct arteriolar vasodilation induced by dipyridamole.

Changes in the coronary microcirculation may also play a role in the observed improvement in perfusion defects. Recently, endothelial-dependent, flow-induced vasodilation of coronary arterioles has been demonstrated in isolated preparations and in intact animals after reactive hyperemia. Atherosclerosis of proximal, conduit, epicardial coronary arteries impairs endothelial-mediated vasodilation of the distal microcirculation. In experimental animals, cholesterol lowering or treatment with fish oil improves the endothelial-mediated vasodilatory capacity of both coronary arteries and distal arterioles. Therefore, the coronary flow response induced by the direct effect of dipyridamole on arteriolar vasodilation may be augmented by a further improved flow-mediated, endothelial-dependent arteriolar vasodilation in response to the initial increased flow caused by the direct effect of dipyridamole.

Based on this reasoning, we also suggest that an additional mechanism for the decreased size and severity of perfusion defects by PET after dipyridamole is improved vasodilation of the microcirculation in patients undergoing vigorous cholesterol lowering.

**Study Limitations**

The most significant complications of the study occurred in the group treated by total parenteral alimentation. Fever and/or infection related to the chronic intravenous alimentation line occurred in 5 of the 7 patients treated by this method at all sites (only 1 patient was recruited among the three non-Houston sites, and his studies were not completed).

At the time of this study, there was no PET protocol or software reported for automatic measurement of absolute coronary flow and flow reserve for routine clinical appreciation. Accordingly, size and severity of perfusion defects after dipyridamole were used as objective end points measured completely automatically without observer interpretation, drawing regions of interest, or visually defining abnormalities on the PET scans. The effects of arterial input and falling extraction at high coronary blood flows were not accounted for. However, correcting for these effects are not necessary for following changes in relative sizes of abnormalities on standard PET images of radionuclide uptake.

Although we have subsequently validated a new PET imaging protocol, kinetic models, and software for completely automated determination of absolute coronary flow (in mL · min⁻¹ · g⁻¹) and coronary flow reserve, this approach is not applicable technically in retrospect to the PET images of this study because the data were not acquired in the format necessary for calculating absolute flow.

Strict dietary reduction of fat to 10% or less of calories is commonly regarded as not attainable by most patients with coronary artery disease. However, a diet of less than 10% of calories as fat has been previously reported in the Life Style Heart Trial to stop progression or reverse coronary artery stenoses in most patients. In the clinic of one of the authors (K.L.G.), such diets are routinely achieved in patients with coronary artery disease by following an individualized approach. A low-fat diet combined with lipid-lowering drugs is associated with relief of angina, partial reversal or stopping progression of stenoses, and prevention of clinical events such as bypass surgery or balloon angioplasty in 75% to 80% or more of patients.

Whether marked cholesterol lowering causes increased deaths because of suicide or trauma has been a concern. However, in the Multiple Risk Factor Intervention Trial, no excessive traumatic deaths were observed. In the Family Heart Study, improvements in diet of a cholesterol-lowering program were associated with reduction in depression and aggressive hostility in parallel with lowered cholesterol levels compared with the control group on a standard high-fat “American
diet.” Therefore, in prospective trials, there is no identifiable risk of increased suicide or traumatic deaths.

Although patients received adequate protein and showed increased exercise capacity, HDL levels followed a downward trend during the treatment period. However, this decrease was not statistically significant and has not been characteristic of other studies of cholesterol lowering. There was no relation between changes in HDL and perfusion abnormalities by PET.

**Clinical Implications**

The present study demonstrates beneficial short-term effects of vigorous cholesterol lowering by decreasing size and severity of perfusion abnormalities on dipyridamole PET images in patients with coronary artery disease. We suggest that these functional changes most likely reflect improved endothelial-mediated, vasodilatory capacity and that improvement in perfusion abnormalities by PET after dipyridamole is therefore a noninvasive marker of healing endothelium as reported to occur in experimental animals after cholesterol lowering. Our study also shows the feasibility of following such changes noninvasively by objective, automated measures of perfusion abnormalities by rest-dipyridamole PET.

These results in a small number of patients suggest that clinical trials of cholesterol lowering should take into account the changes in myocardial perfusion reflecting the integrated flow capacity of the entire coronary arterial/arteriolar vascular system by objective, automated quantitative PET in addition to changes in focal arteriographic stenoses that do not account for diffuse coronary atherosclerosis or associated functional vasomotor abnormalities.

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