Myocardial Perfusion after Cholesterol Lowering

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In recent randomized trials, vigorous cholesterol lowering by moderate low fat diet and cholesterol lowering drugs or intensive lifestyle change resulted in stopping progression or partial reversal of coronary artery disease in up to 80% of treated subjects. The regression in these recent trials was only modest, 3% to 10% diameter stenosis units depending on stenosis severity at baseline, but was consistently observed and statistically significant. There was a proportionately larger, major decrease in clinical events of myocardial infarction, death, bypass surgery or balloon angioplasty in up to 80% of the treatment groups undergoing vigorous cholesterol lowering compared to control groups. The reason for proportionately greater clinical benefit than extent of anatomic regression appears due to plaque stabilization and reduction in the risk of plaque rupture which leads to acute unstable coronary syndromes, particularly at sites of relatively mild narrowing in diffusely atheromatous coronary arteries. There is also a marked decrease in angina pectoris in parallel with decreased coronary events. Therefore, dietary and pharmacologic cholesterol lowering provides an alternative approach to the treatment of coronary atherosclerosis that substantially reduces the necessity for balloon angioplasty or bypass surgery.

Although used as a measure of changing stenosis severity in lipid lowering trials, percent diameter narrowing by coronary arteriography does not account for complex shape changes of stenoses, is poorly related to flow capacity or coronary flow reserve and fails to account for diffuse disease present in most patients with or without localized coronary artery narrowing. The degree of improvement of percent stenosis in regression trials is quite modest ranging up to 5% diameter stenosis units for all stenoses and up to 10% diameter stenosis for more

severe stenoses. Based on automated, objective quantitative analysis of PET images before and after vigorous cholesterol lowering, the size and severity of myocardial perfusion abnormalities by PET after dipyridamole stress decrease or improve in patients undergoing intense lifestyle changes and/or treated with cholesterol lowering drugs in comparison to an increase or worsening in patients treated with standard anti-anginal therapy alone (1-4). The improvement in perfusion abnormalities on PET images after vigorous cholesterol lowering demonstrates the functional changes in the atherosclerotic coronary arterial tree associated with the modest extent of anatomic regression by arteriography after cholesterol lowering.

Vigorous cholesterol lowering by extreme dietary restriction or cholesterol lowering drugs over a relatively short time of 90 days improves myocardial perfusion in patients with coronary artery disease before anatomic regression occurs (1). Within 60 days after discontinuing lipid lowering treatment, size and severity of perfusion abnormalities by PET return to baseline control status. These rapid changes in perfusion indicate changing vasomotor function rather than anatomic regression or progressive of stenoses in such short time periods.

Myocardial perfusion abnormalities by PET at resting conditions also improve with lipid lowering. If the baseline perfusion defects in the population studied are fairly severe or patients are followed for a sufficiently long time for substantial changes to occur, e.g. 5 years, the changes in stress perfusion scan are greater than the changes in the rest perfusion scans due to anatomic changes in stenosis severity (1). However, if the baseline perfusion abnormalities are less severe and followed for a shorter period with less time for change or with less vigorous lipid intervention, e.g. 2 years, then rest perfusion images may show greater changes than stress images (3). Mild stenoses of 40% to 50% diameter narrowing cause only mild reduction of coronary flow reserve. Therefore, substantial diameter changes of mild stenoses, e.g., 40% to 50% diameter narrowing or vice versa, do not cause significant changes in coronary flow reserve that can be

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This article was presented at the 28th Annual Meeting on the Japan Atherosclerosis Society in Osaka, 1996.

Received November 11, 1996.

imaged clinically. In contrast, small changes in the diameter of more severe stenoses show profound effects on coronary flow reserve due to arterial flow being proportional to arterial radius raised to the fourth power.

Therefore, the explanation for rest-stress differences in different studies is that changes in endothelial function associated with cholesterol lowering may alter resting vasomotor function and resting perfusion more than the relatively minor effect of changing mild stenoses on maximum perfusion or coronary flow reserve. For milder stenoses that do not alter coronary flow reserve significantly, resting PET images show effects of cholesterol lowering on resting vasomotor tone and perfusion. For more severe stenoses, dipyridamole PET images show the effect of cholesterol lowering on coronary flow reserve reflecting both anatomic regression and improved endothelial function.

Several additional reports confirm our observation on changes in myocardial perfusion and coronary flow reserve. Maximum myocardial perfusion measured in cc/min/gm and absolute coronary flow reserve by PET improve in direct proportion to the fall in serum cholesterol levels over six weeks of physical training and low fat food (5). Again, the improvements in perfusion over such a brief time of 42 days implies altered vasomotor function rather than anatomic changes in the coronary arteries. Although less reliable and less quantitative than PET due to attenuation and technical imaging limitations, exercise perfusion imaging by single photon emission computer tomography (SPECT) shows less severe perfusion defects in patients with coronary artery disease after exercise training and low fat diet (6). Short term lowering of cholesterol over 12 weeks by fluvastatin also decreases the severity of perfusion abnormalities on exercise perfusion images by (SPECT) (7).

The improvement in size and severity of myocardial perfusion abnormalities after dipyridamole stress in patients undergoing cholesterol lowering in comparison to worsening in controls most likely involves two mechanisms. The first, occurring over one or more years, is partial anatomic regression of localized coronary artery stenosis, as previously demonstrated by quantitative coronary arteriography. Although not documented, this anatomic regression probably also involves regression of diffuse narrowing throughout the length of the artery since risk of plaque rupture is diminished.

A second mechanism for decreased size and severity of perfusion abnormalities by PET is improved endothelial mediated, coronary artery and arteriolar vasodilation both at resting conditions and in response to high flows after initial direct arteriolar vasodilation induced by dipyridamole. In primates with coronary atherosclerosis, this improvement in endothelial mediated vasomotor function of the coronary vasculature after cholesterol lowering precedes anatomic regression. Our observations of improved perfusion with smaller abnormalities by PET imag-

ing in humans relatively rapidly after cholesterol lowering are consistent with experimental studies in animals showing restoration of endothelium-dependent vasodilation by dietary fat restriction and/or cholesterol lowering. Our observations of improved stress perfusion defects by PET after five years of lipid lowering indicate anatomic regression of stenoses in addition to improved rest perfusion defects reflecting improved endothelial mediated vasomotor function.

Coronary arteriography has been the basis for documenting stabilization or partial reversal of stenoses after cholesterol lowering. The proportionately greater decrease in cardiovascular events combined with improved symptoms is the basis for the comprehensive, principally non-invasive management of coronary heart disease (4). However, reliance on coronary arteriography for diagnosis of, and following changes, in coronary artery disease precludes primarily non-invasive management. However, PET perfusion imaging is as good as coronary arteriography for diagnosis with sensitivity and specificity of 95% (4). Disagreements between PET and arteriography are usually due to over reading severity of arteriographic percent narrowing or missing diffuse disease that causes no segmental narrowing. PET is also as good or better than coronary arteriography for following changes in disease severity (1). Consequently, in the author's clinical practice PET perfusion imaging has become the basis for the comprehensive non-invasive diagnosis, management and follow-up of coronary heart disease using vigorous reversal treatment.

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