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The Clinical Importance of Risk Factor Modification: Looking at Both Myocardial Viability (MV) and Myocardial Perfusion Imaging (MPI)

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Abstract. Determination of changes in coronary artery disease (CAD) following risk factor modification (lipid lowering and stress reduction) have focused only on changes in myocardial blood flow (Q)/myocardial perfusion imaging (MPI) and not myocardial viability (MV). To determine the outcome of each and to determine if there are differences in myocardial viability versus coronary blood flow, 31 people were studied for 1 year with comparison of baseline and 1-year PET results. One subject underwent an additional 2-year follow-up study, providing a total of 32 comparisons. A total of 224 myocardial segments were compared with improvement in MPI seen in 58 of 224 segments (25.9%), stabilization in 111 of 224 (49.6%) segments, and progression of disease in 55 of 224 (24.6%) segments. MV improved in 82 of 224 segments (36.6%), showed stabilization in 83 of 224 (37.0%) of the segments, and worsening in 59 (26.3%) of 224 segments. When improvement in either MPI or MV were added together, improvement was seen in 50.9% ($p \leq 0.001$) of the segments and stabilization was seen in 30.4% ($p \leq 0.001$). Despite RFM as defined above, progression of CAD and loss of myocardial viability was noted in 15% of the myocardial segments studied. This study demonstrated that regardless of whether one looks at MPI alone or a combination of MPI and MV, reduction of serum lipids and stress reduction alone cannot guarantee stabilization or regression of atherosclerosis. Clearly there are additional factors involved which play an important role in reveral of CAD which must be addressed in future studies.

Introduction

Studies investigating risk factor modification (RFM) including dietary changes [1–5] have clearly demonstrated improvement in coronary blood flow using positron emission tomography (PET), single photon emission computed tomography (SPECT), and quantitative coronary arteriography (QCA). However, this previous work has not addressed the issue of myocardial viability (MV), which must be considered since MPI and MV are distinctly different issues.

To answer the question about the success of current RFM approaches it is necessary to determine the effect upon *both* MPI and MV. This is the first study designed to answer that question. To do this a total of 31 people were studied for 1 year, and one person for 2 years. Seven myocardial regions were compared both at the beginning and end of the study to determine if changes in MPI or MV occurred following treatment. This study was also designed to determine if differences in outcomes varied between the different myocardial regions represented by the left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA) regions.

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Methods

Thirty-one participants with elevated cholesterol levels were enrolled in a RFM program as previously described [2] in an effort to reduce their overall risk of CAD. One of the patients underwent a third study at the end of the second year, for a total of 32 paired studies. Each participant underwent a standardized PET imaging protocol as described previously [6] using nitrogen-13 ammonia (NH_{13}) to determine changes in Q/MPI and fluorine-18 2-fluoro-2-deoxyglucose (FDG) to assess changes in MV. The protocol used is outlined in Figure 1.

PET Image Interpretation

The analysis of MPI (NH_{13}) and MV (FDG) was made for seven regions of myocardium for each study in question for a total of 224 segments. The seven regions are shown in Figure 2, and include the anterior (ant), anteroseptal (A/S), posteroseptal (P/S), inferoposterior (I/P), posterolateral (P/L), anterolateral (A/L), and apical (apex) regions. Qualitative assessment of each region was made using a six-point rating scale with 0 equaling no tracer activity, 1 = severe perfusion defect, 2 = moderate defect, 3 = mild defect, 4 = probably normal, and 5 = normal perfusion. An example of the grading scale and the rating form is shown in Figure 2. Images were graded at rest and following stress for NH_{13} and at rest for FDG. An example of the grading protocol used for a resting image is shown in Figure 2.

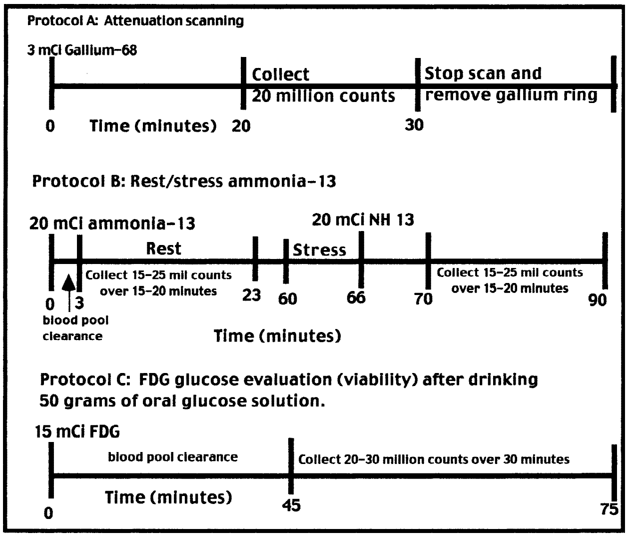

Fig. 1. PET imaging protocols used to assess MPI and MV. Following attenuatioin correction (protocol A), perfusion of myocardial segments (protocol B) is performed first at rest, then stress using NH_{13}. Myocardial viability (protocol C) is determined using FDG.

Each image was interpreted by a board-certified nuclear cardiologist (also certified in PET imaging), independent of any clnical data, name of patient or other information regarding the sequence of the image being interpreted. Images were not paired for comparison reading. Each of the PET images were randomly arranged and interpreted twice (once on two different occasions) in different orders for each reading, with the results averaged. The averaged results of baseline and 1-year studies were then compared for changes for both MPI and MV.

Statistical Analysis

Following the interpretation for each image a nonparametric Wilcoxon analysis was performed to determine the validity of interobserver readings for each of the PET Images interpreted. These results were then compared between baseline and 1 year for each of the three epicardial coronary arteries (LAD, LCx, and RCA) and for each of the seven myocardial regions using chi-square analysis to determine if there were any outcome differences in the various arterial distributions. Finally, chi-square analysis was used to determine differences between results obtained via MPI, MV, and both MPI and MV combined.

Table 1. Changes in MPI, and MV in each of the three major epicardial coronary arteries

	Improvement			No change			Deterioration		
	MPI	MV	χ^2 value	MPI	MV	χ^2 value	MPI	MV	χ^2 value
LAD	28	57	0.001	76	43	0.001	24	28	NS
LCx	20	12	NS	24	33	NS	20	19	NS
RCA	10	13	NS	11	7	NS	11	12	NS
All	58	82	0.01	111	83	0.01	55	59	NS

LAD = left anterior descending artery, LCx = left circumflex artery, RCA = right coronary artery, All = all three arteries, NS = not statistically significant.

Results

The results of Wilcoxon nonparametric analysis of the interobserver variability of PET image interpretation showed no statistical differences between the first and second readings. There were no statistical differences between interobserver readings of the seven myocardial regions, or between the various isotopes used (NH_{13} or FDG) in the study. Additionally, there were no statistical differences between images interpreted following “stress” and those performed at “rest.”

When MPI (Table 1) alone was looked at, improvement was seen in 25.9% (58 of 224) of the arteries. No change was seen in 49.6% (111 of 224) of the arteries and deterioration was seen in the remaining 24.6% (55 of 224). While there was no statistical difference in deterioration or progression of CAD as assessed by MPI or MV (p = NS) as shown in Table 1, there was a statistical shift from no

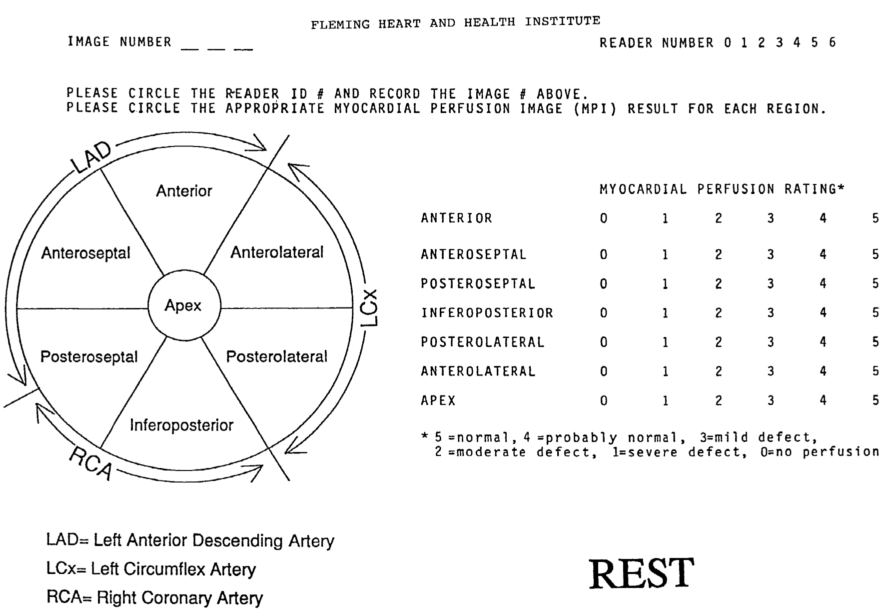

Fig. 2. PET grading protocol. Each study (rest, stress, viability) is analyzed independently for positron tracer activity using a six-point grading scale for each of seven regions of myocardium. These seven myocardial segments were later matched to epicardial artery regions as shown in the diagram.

change in MV in the LAD artery towards improvement ($p < 0.001$). This difference was not seen in the LCx or RCA arteries.

When both MPI and MV (Table 2) were taken into consideration, improvement was seen in both the LAD ($p < 0.001$) and right coronary ($p < 0.01$) arteries. However, despite looking for improvement in either MPI or MV, progression of disease was documented in both MPI and MV in 15% (35 of 224) of the arterial segments.

An example of a 32-year-old patient is shown in Figure 3. This image shows the results of a "stress" image at baseline with MPI decreased in the anterior, apical (LAD), and inferior (RCA) regions of the heart. The baseline MV study is shown in the second picture (B) with reductions in FDG activity (MV) in the same myocardial segments. As shown in image C, the MPI at "stress" revealed no significant change in blood flow 1 year later. The final image (D) shows an improvement in FDG activity (MV) in the anterior

Table 2. Changes in MPI versus MPI and MV in each of three major epicardial coronary arteries

	Improvement			No change			Deterioration		
	MPI	MPI or MV	χ^2 value	MPI	MPI or MV	χ^2 value	MPI	MPI or MV	χ^2 value
LAD	28	67	0.001	76	43	0.001	24	14	0.05
LCx	20	28	NS	24	18	NS	20	16	NS
RCA	10	19	0.01	11	7	NS	11	5	NS
All	58	114	0.001	111	68	0.001	55	35	0.01

LAD = left anterior descending artery, LCx = left circumflex artery, RCA = right coronary artery, All = all three arteries, NS = not statistically significant.

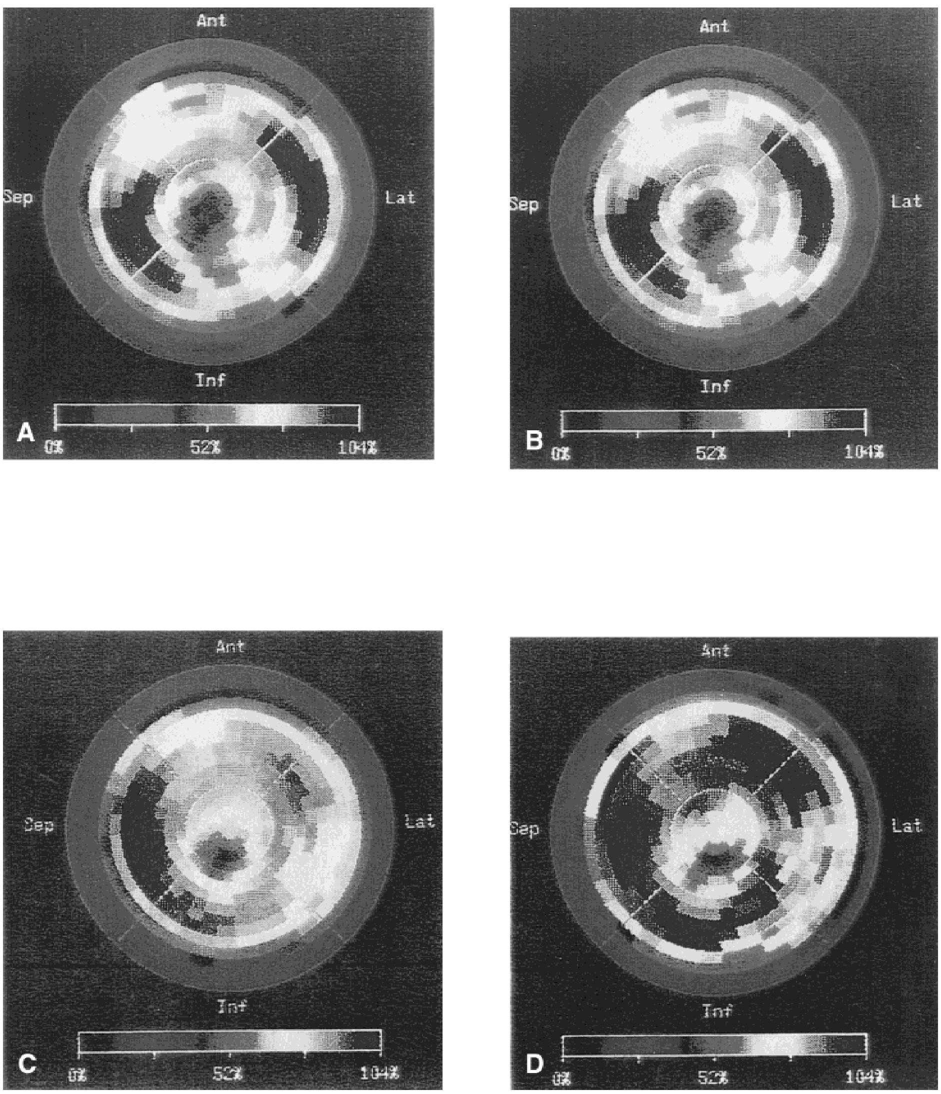

Fig. 3. Example of a PET study. Image A show the baseline "stress" study where NH_{13} is used to study MPI. Tracer activity is represented by a grey scale where white represents greatest activity, and black being the least. All images are presented as "bullseye equivalent" images with the top part of the image representing the anterior region (ant), the bottom of the image represents the inferior (inf) region of the left ventricle, while the 9 o'clock position represents the septum (sep) and the 3 o'clock position represents the lateral wall of the heart. In the initial PET image, activity is decreased anteriorly, inferiorly, and apically. Image B shows MV as determined by FDG activity. The anterior, apical, and inferior regions supplied by the LAD and RCA demonstrate decreased MV. Image C shows the results of MPI following "stress" 1 year later. There is no difference in myocardial blood flow following 'stress' image acquisition over the course of one year of treatment (image C versus image A). However, MV imaging after one year of treatment (image D) demonstrated considerable improvement in all regions when compared with image B, except for the apex where prior myocardial infarction was seen in both studies.

and inferior regions. The apical region continues to show severely decreased activity consistent with a prior myocardial infarction, noted on the original study.

Table 3 shows differences in myocardial regions comparing the results obtained when looking at MPI versus MPI and MV. These results are consistent with that shown in tables 1 and 2 and demonstrate that the shift in MV is seen primarily in the anteroseptal (A/S) and posteroseptal (P/S) regions of the heart.

Discussion

The consistency of PET interobserver readings in a board-certified nuclear cardiologist with specialized training in PET imaging and interpretation is the first such report looking at PET interobserver variability including information on both isotopes and region of myocardium in question. Further work looking at reader experience, isotopes, camera type, and type and form of "stress" is currently being completed.

Table 3. Changes in MPI and MV by region of myocardium

	Improvement			No change			Deterioration		
	MPI	MPI or MV	χ^2 value	MPI	MPI or MV	χ^2 value	MPI	MPI or MV	χ^2 value
Ant	10	15	NS	15	7	NS	7	10	NS
A/S	4	12	0.001	25	17	NS	3	3	NS
P/S	5	15	0.001	22	11	0.05	5	6	NS
I/P	10	13	NS	11	7	NS	11	12	NS
P/L	11	6	NS	10	16	NS	11	10	NS
A/L	9	6	NS	14	17	NS	9	9	NS
Apex	9	6	NS	14	17	NS	9	9	NS
Total	57	82	0.001	110	83	0.05	57	59	NS

Ant = anterior, A/S = anteroseptal, P/S = posteroseptal, I/P = inferoposterior, P/L = posterolateral, A/L = anterolateral, NS = not statistically significant.

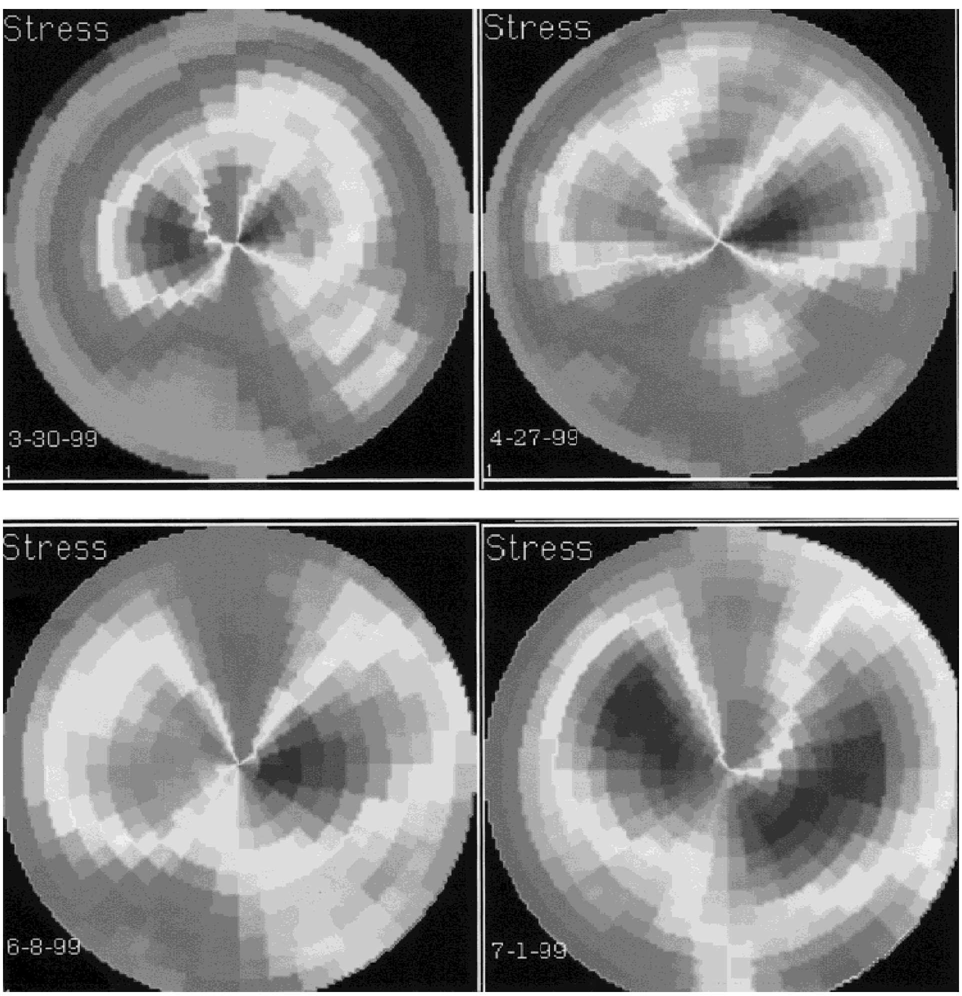

Fig. 4. Treatment of heart disease with interleukin inhibitor and antibiotics. Four bullseye images following high-dose dipyridamole (HDD) maximal pharmacologic "stress" are displayed with maximal tracer (blood flow activity) represented as white with the least amount of blood flow represented by black. Decreased blood flow is represented by darker shades of grey on the grey scale images. Each image displays the anterior wall at 12 o'clock, the lateral wall at 3 o'clock, the inferoposterior region at 6 o'clock, and the septal wall at 9 o'clock. The top two images reveal decreased perfusion (not shown here) anteriorly and posteroseptally in the image marked 3-30-99. Four weeks later, these areas (image marked 4-27-99) reveal improved blood flow following treatment with accolate (interleukin inhibitor) and L-arginine.

In the bottom row of images a 50-year-old woman was treated for *H pylori* infection. Following 1 week for test results and 2 weeks of antibiotic treatment (pretreatment is 6-8-99 and posttreatment is 7-1-99), there is almost complete resolution of the posteroseptal (RCA) disease and ~50% improvement in the anterior disease (LAD). In both cases myocardial viability also improved based upon resting Sestamibi studies.

The utilization of MPI to determine coronary blood flow has typically been used to look for coronary ischemia and infarction. Despite the importance of myocardial viability, MV has not been previously addressed in RFM studies. The outcome of MV is different from that of MPI suggesting that the first observable effect of RFM is recovery of "stunned/hibernating" myocardium and not dramatic differences in percent diameter stenosis or MPI. This is to be expected since at least theoretically during the early stages of recovery, remodeling probably plays the major role in response to RFM versus simple plaque regression. Regardless of whether these differences represent "stunned" or "hibernating" myocardium, or some other process may not be as important as realizing the clinical significance of improvement in MV, which can occur in the absence of significant changes in Q/MPI.

While reversibility in one segment of the heart does not guarantee successful outcomes in another region, the data demonstrate the importance of looking for both MPI and MV in each myocardial region. Improvement in coronary diameter (blood flow/Q) without improvement in the myocardium (viability/life) itself is less significant than improvement in both, since heart failure and cardiac morbidity are directly related to the viability of the myocardium. Similarly, improvement in MV without substantial change in Q, suggests myocardial salvage (eg, stunned/hibernating myocardium) for the present, but with increased risk of future morbidity and mortality resulting from the persistently inadequate coronary blood flow.

Conclusion

Clearly other factors above and beyond lipids and stress reduction are involved in both the progression and regression of atherosclerotic disease. As shown in Figure 4, other factors which must be addressed include (at least in some cases) interleukins and bacterial infections. The results of this study adds further support to the argument that other factors [7] must be addressed to successfully control vascular disease whether it be coronary, carotid, or elsewhere in the body.

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