Angiology
Volume X Number X
Month XXXX xx-xx

10.1177/0003319707303887
http://ang.sagepub.com
hosted at
http://online.sagepub.com

What Is the Relationship Between Myocardial Perfusion Imaging and Coronary Artery Disease Risk Factors and Markers of Inflammation?

Richard M. Fleming, MD, and Gordon M. Harrington, PhD

The treatment of coronary artery disease (CAD) is clinically measured by monitoring changes in venous lipids and inflammatory markers. There is currently no established quantified relationship between coronary flow reserve and markers of inflammatory CAD. A total of 120 men and women underwent quantified measurement of coronary blood flow using SPECT imaging at baseline and 1 year later. They had fasting venous blood work obtained at baseline and 1 year later. These markers of lipids and inflammation included, total cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, lipoprotein-a, homocysteine, fibrinogen, C-reactive protein, and interleukin-6. Regression analysis reveals no general statistical relationship between these markers and coronary blood flow as measured by myocardial perfusion imaging. However, when changes in indices are considered and changes in risk factors are compared with changes in ischemia, blood factor based estimates yield an adjusted $R^2 = 0.31$, $R = 0.57$, $P < .0001$. Initial levels of coronary ischemia cannot be diagnostically inferred from baseline values in lipid and inflammatory markers of coronary artery disease. When change in coronary blood flow is quantified using SPECT imaging, 6 independent underlying blood factors provided statistically useful information in identifying changes in coronary blood flow. Although the relationship of changes is statistically significant ($P < .0001$), quantification of coronary blood flow by SPECT imaging provides physiologic status information, which cannot be inferred from fasting markers of lipids and inflammation status.

Keywords: myocardial perfusion imaging (MPI); CVD risk factors; Lipids; inflammation and coronary artery disease

Both anatomic and physiologic tests are carried out to evaluate coronary artery disease (CAD). Anatomic tests include cardiac catheterization, intravascular ultrasound, coronary artery calcium scores, and so on. Physiologic tests include exercise stress testing, positron emission tomography (PET), and single photon emission computed tomography (SPECT)[1] imaging. Sophisticated computer programming is used in PET and SPECT to determine differences in the uptake of isotope during imaging, which are dependent on coronary blood flow.[2-6] Although black and white or color imaging is used in most of the SPECT studies to qualitatively determine differences in isotope activity, allowing physicians to determine whether injury/infarction (rest imaging) or CAD following stress (exercise or pharmacologic) imaging is present, these studies can be quantified to determine regional blood flow differences (CAD) that explain angina.[7,8]

During the last decade, it has become increasingly obvious that we need to broaden the type of testing performed to determine whether CAD is present, and to determine the underlying cause of this inflammatory disease. To that end, we and others have been looking at a variety of markers

From the Critical Care and Cardiology, Department of Internal Medicine, Sierra Nevada Veterans Affairs Health Care System, Reno, Nevada (RMF), and Department of Psychology, University of Northern Iowa, Cedar Falls, Iowa (GMH).

Address correspondence to: Richard M. Fleming, MD, Sierra Nevada Health Care Systems, Veterans Affair Hospital, Department of Internal Medicine, Division of Cardiology, 1000 Locust Street (111), Reno, Nevada 89502-2597; e-mail: rmfmd7@hotmail.com

designed to better understand the inflammatory process associated with CAD and acute coronary syndromes (ACS).[9-19] Little, if any, information exists regarding the relationship between conventional (lipids) and newer (inflammatory) blood markers of CAD and myocardial perfusion imaging (MPI) itself. Because physicians have been encouraged to treat the CAD risk factors and measure changes in lipid and inflammatory markers following treatment, it is assumed that these changes correlate with changes in coronary blood flow. Although a clinically important assumption, these baseline markers of CAD, along with changes in these markers, have not previously been compared with quantified MPI. This is partially the result of MPI being used as more of a qualitative than quantitative tool and partially the assumption that lowering a risk factor for heart disease automatically improves the coronary blood flow.

The purpose of this study was to determine which of the venous markers, which measure lipids and inflammation, are most predictive of heart disease and to investigate the relationship between coronary blood flow and the blood chemistry heart risk factors that we treat, under the assumption that treating these risk factors will result in an improvement in coronary blood flow. Therefore, we studied 120 volunteers who were not using statins or other medications known to affect lipids, initially and after 1 year. We specifically asked the following questions: (a) How are the 11 venous markers of lipids and inflammation associated with coronary blood flow? Specifically, is blood chemistry, as measured by a lipid profile and markers of inflammation, diagnostically associated with coronary blood flow status as measured quantitatively by MPI derived ischemic index. (b) Are changes in the blood chemistry profile are associated with changes in the coronary blood flow? (c) What are the factors underlying changes in the blood chemistry profile?, and (d) How are those underlying factors associated with blood flow changes?

Methods

Enrollment

One hundred and twenty men (n = 63) and women (n = 57) with multiple risk factors for CAD who were between 30 to 59 years of age were enrolled in a treatment program for inflammatory heart disease. Study participants were consented for the study using standard institutional consent forms. Participants were excluded from the study if they were taking statin or other medications known to affect lipids, werepregnant, or had cancer, diabetes mellitus, liver disease, renal disease, or gastrointestinal disease.

Fasting Venous Blood Work

Fasting blood work was carried out at the beginning and after 1 year of the study. This included total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, triglycerides, homocysteine (Hcy), fibrinogen (Fib), C-reactive protein, interleukin-6 (IL-6), and lipoprotein-a (Lp). The methodology for determining these variables has been described in detail elsewhere[20-22] with the exception of IL-6, which was measured from fasting venous blood samples, were immediately spun, separated, and then frozen for enzyme-linked immunosorbent assay.

Myocardial Perfusion Imaging

Study participants were imaged at the beginning and at the end of the 1-year study using the following methods that have been mentioned previously.

Pharmacologic Stress

Dipyridamole was used to induce coronary vasodilation as shown in Figure 1. This approach has been reported previously in our lab[23-27] to produce the desired changes in coronary flow reserve (CFR) and quantification of regional blood flow differences. As noted, the amount of dipyridamole and sestamibi administered is based on the total body weight of the subject.

SPECT Equipment

Myocardial perfusion imaging was performed using a Siemens orbiter model 6601 (Siemens, New York, NY), 75 photomultiplier tube SPECT camera as described in detail previously.[23-27] A low energy high-resolution collimator was used with a 20% window and a 100 by 100 matrix. A step and shoot approach was used at 60 seconds per each of 32 views rotating 180 degrees beginning in the right anterior oblique and ending in the left posterior oblique position for a total of 34 minutes acquisition time. Images were reconstructed using standard back projection with reconstruction of short-axis, horizontal

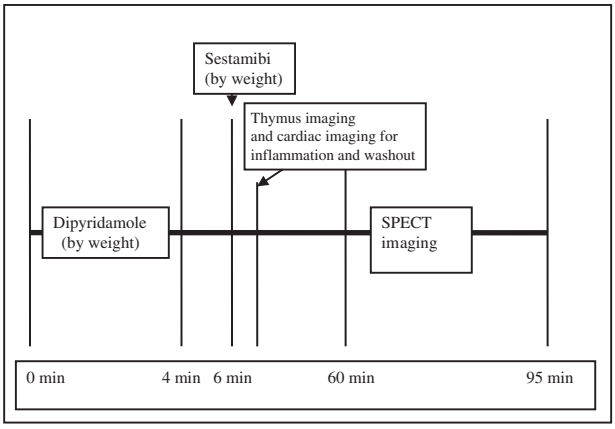

Figure 1. Protocol for pharmacologic vasodilation of coronary blood flow to enhance coronary flow.As described in detail elsewhere, patients are brought into the nuclear lab for imaging in a fasting state with prior placement of an IV catheter into either in the right or left upper extremity. Through the IV, they are given an infusion of dipyridamole for 4 minutes continuously based on actual body weight. At 6 minutes, 25 to 30 mCi of sestamibi is introduced followed by a 12 to 20 cc flush of normal saline. Thymus and cardiac imaging to assess possible inflammation and washout related to coronary artery disease begins 5 to 10 minutes after sestamibi injection. One hour after the beginning of the study, the patient is placed under the camera where images are acquired over the next 34 minutes. The person is then allowed to leave after removal of the IV. Reconstruction and processing of the information obtained then begin, with final results as shown in Figures 2A and 2B.

and vertical long-axis, and bull's-eye views. Quantification of bull's-eye images was completed as described below.

Ischemic Index

Following dipyridamole stress and image acquisition and reconstruction, specialized software was used to quantify reductions in coronary flow. Figure 2A shows the distribution of epicardial coronary arteries with that of myocardial regions. As shown in Figure 2B, regions of interest (ROIs) can be defined to determine the amount of isotope activity present in each ROI. This information can be further defined based on the amount of activity present per pixel per millicurie of isotope given to the patient. Using this specialized software, qualitative representation of coronary flow is shown, (Figure 2C) where red represents the maximal coronary flow with less flow shown with yellow and green, respectively. This qualitative approach is typically used by clinicians to determine the presence or absence of CAD. However, the computer produces this qualitative assignment of color based on quantitative information typically not looked by the physician or diagnostician. Again, as the computer uses the software equipment to assign these colors, one can ask for and obtain quantified information about isotope counts for the entire myocardium. From this information, the computer can determine regions (extent) of reduced isotope (flow) activity and the significance of the reduction (severity) in isotope flow. As shown in the lower panel of Figure 2B, the computer software can measure and define the extent and severity of reduced flow for each of the regions of myocardium requested. When the extent of flow reduction is multiplied by the severity of flow reduction, ischemia for that area can be determined as shown in Figure 2C. When each of these areas are added together, the total ischemic (ischemic index, II) burden of the heart can be determined, providing quantitative measurement of coronary flow.

Statistical Analysis

To determine the relationship between the various venous blood tests that measure lipids and inflammation, a simple linear regression analysis of these 11 blood tests and the ischemic index was made. To determine the relationship between the change in these 11 blood tests and ischemia, the measures were first standardized to facilitate reading tables. Both principal components and varimax factor analyses of these venous markers were used to determine which of these variables accounted for the majority of variance and also to reduce dimensionality. With multiple predictive tests, one asks whether the tests represent multiple sources of the same information or sources of different information. Principal components show the dimensional reduction attainable. Factor analysis estimates the relative contributions of the presumed underlying variables. A simple regression analysis was then performed on these factors. The resulting fitted predicted values are a composite of the blood test profiles. The fit was evaluated using a simple standardized regression of the observed ischemic index on the predicted values, the composite blood profile. Generally, outliers and other deviations from the linear model tend to reduce the power of the multivariate linear model so that it is usually more conservative than are more distribution free procedures. However, to assess the anticipated effects of such deviations, the standardized composite regression coefficient and correlation between the 2 variates was compared with

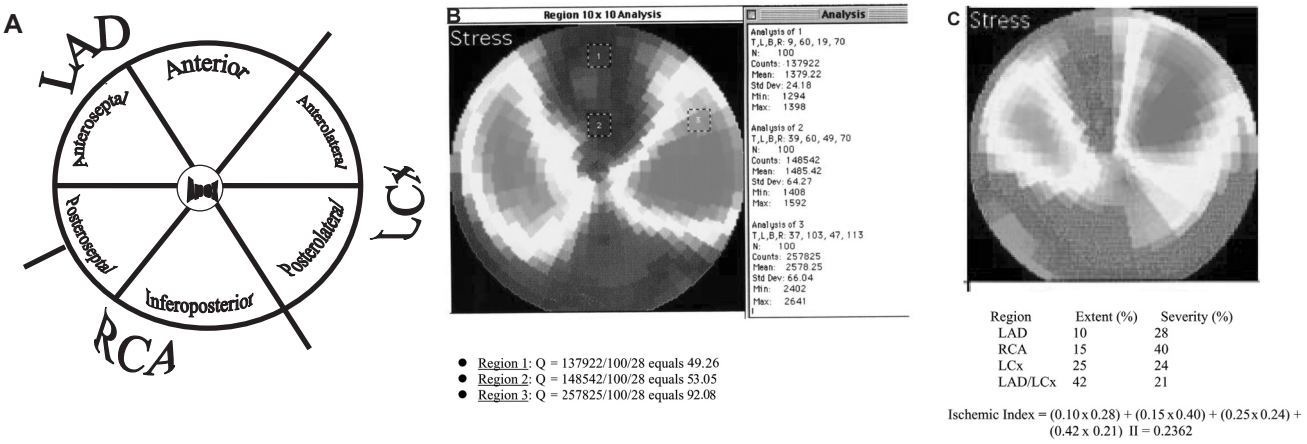

Figure 2. A, Bull's-eye (clock face) representation of reconstructed images following SPECT image acquisition.Reconstruction of MPI into a clock face or Bull's-eye representation displays the entire myocardium along with its representative epicardial coronary arteries, including the LAD,which perfuses the anterior, anteroseptal, apical, and portions of the posteroseptal myocardium. The LCx artery perfuses the anterolateral and posterolateral myocardium. The RCA supplies the inferoposterior and portions of the posteroseptal myocardium as shown. B, Quantification of isotope activity using SPECT imaging.This bull's-eye display of isotope flow (Q) shows how ROIs are quantified. Three ROIs are shown, each of which represent 10 × 10 pixels for a total pixel area of 100 (N = 100). To the right of the color image, the actual radioactive counts, the mean + standard deviation of these counts, and the minimal and maximal counts throughout the ROI are shown. The isotope flow is further standardized by measuring the radioactive counts (C)/number of pixels per ROI (P)/the number of millicuries (M) of isotope administered (CPM). As shown, the flow (Q) in region 1 is less (49.26) than region 2 (53.05); however, qualitatively both regions are displayed as green on the color coded image. The third region is displayed in red and quantitatively shown to have the greatest amount of isotope (blood) flow with a value of 92.08 CPM. C, Determination of ischemic index (II) by quantification of MPI. Qualitative determination of regional perfusion differences determined by color scale as shown here is a frequent method of MPI interpretation. Nuclear computers assign colors based on quantitative information obtained by the camera. This same information can be seen by the investigator when asked for as shown in this figure. This example shows 4 regions perfused by the epicardial arteries, including the LAD artery, the RCA, the LCx artery, and the region supplied by both the LAD and LCx arteries, which are sometimes referred to as the watershed zone or region. Each region accounts for a portion of the entire myocardium. All 4 regions added together account for 100% of total myocardial blood flow. When each arterial region is taken into account, it represents a certain extent of the entire myocardium. Within that region, a reduction in blood flow can be quantified to determine both the amount (extent) of the region involved and the severity (reduction in isotope flow) of disease in that region, yielding an ischemic index (II) for the given artery. When all of these regions of ischemia (II) are added together, a total ischemic index (II) for the heart is determined as shown in the figure. MPI indicates myocardial perfusion imaging; ROIs, regions of interest; IV, intravenous; LAD, left anterior descending; RCA, right coronary artery; LCx, left circumflex.

distribution free estimates using both rank-order (Kendall) and rank-difference (Spearman) methods. Because the data can be rescaled by centile to a N (0,1) distribution, the rescaling would retain the rankings and the method assumptions would be met. All data analyses were carried out with R2.2.1.

Results

Regressing the initial presenting ischemic index on 11 blood tests for lipids and inflammation showed absolutely no statistical relationship between initial lipid and inflammatory marker values and the results obtained with MPI and measurement of ischemia. As shown in Table 1, $P = .38$, $R^2 = 0.0078$.

Having found that risk factors are not diagnostic of blood flow status, it is a different question to ask whether changes in risk factors are associated with changes in blood flow. Table 2 shows the results of both linear and robust regression analysis of changes in ischemic index as a function of changes in risk factors. Regression coefficients are shown for both the linear analysis and the robust analysis, standardized to facilitate interpretation. The residual standard error is smaller for the robust than for the simple analysis. The pattern of magnitudes appears very similar for the 2 analyses. Proceeding with the simple model probably somewhat understates the true magnitude of effects.

Because of the structure of the intercorrelations between indices and despite standardization, visual inspection does not lead readily to a meaningful interpretation of the regression coefficients. To reduce dimensionality of the blood profile, principal components analysis yielded a screeplot showing

Table 1. Pretest Regression of a Nuclear Image Derived Index of Coronary Blood Flow (Ischemic Index) as Estimated From Blood Chemistry Risk Factors[a,b]

Coefficients	Estimate	Standard Error	*t* Value	Pr (>|*t*|)
(Intercept)	–1.252e-01	1.952e-01	–0.641	0.5228
TC	–2.337e-03	5.781e-03	–0.404	0.6868
LDL	2.746e-03	5.821e-03	0.472	0.6380
LowHDL	3.928e-03	7.570e-03	0.519	0.6049
TC/HDL	6.978e-04	2.928e-02	0.024	0.9810
TG	4.751e-04	1.370e-03	0.347	0.7294
TG/HDL	1.374e-04	4.036e-02	0.003	0.9973
CRP	3.062e-04	2.725e-03	0.112	0.9107
IL	–8.593e-04	1.466e-03	–0.586	0.5591
Hcy	–3.011e-04	6.488e-04	–0.464	0.6436
Fib	1.749e-04	7.745e-05	2.259	0.0259
Lp	4.030e-04	4.458e-04	0.904	0.3680

Note: TC, total cholesterol; LDL, low-density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; CRP, C-reactive protein; IL, interleukin; Hcy, homocysteine; Fib, fibrinogen; Lp, lipoprotein.

[a]Residuals: –0.1057 (Min), –0.0352 (1Q), –0.0057 (Median), 0.0267 (3Q), 0.1529 (Max).

[b]No statistically significant (Bonferroni) coefficients; residual standard error: 0.05342 on 108 degrees of freedom; multiple R^2: 0.09955, adjusted R^2: 0.007837; F-statistic: 1.085 on 11 and 108 DF, *P* value: .3798.

Table 2. Comparison of Linear and Robust Regression of Standardized Indices of Nuclear Image Derived Coronary Blood Flow 1-Year Changes on Standardized 1-Year Changes in Blood Chemistry Risk Factors[a,b]

Coefficients	Linear	Robust
(Intercept)	0.0	–0.0671
TC	–3.0460	–2.5141
LDL	2.7440	2.1774
LowHDL	0.1684	0.0697
TC/HDL	0.2819	0.2947
TG	1.4230	1.2793
TG/HDL	–0.6348	–0.7153
CRP	–0.0134	–0.0331
IL	0.0502	0.0301
Hcy	0.0579	0.0544
Fib	0.1746	0.1098
Lp	0.0542	0.0462
Residual standard error	0.8327	0.5533

Note: TC, total cholesterol; LDL, low-density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; CRP, C-reactive protein; IL, interleukin; Hcy, homocysteine; Fib, fibrinogen; Lp, lipoprotein.

[a]Residuals—Linear: –2.2006 (Min), –0.3913 (1Q), –0.0399 (Median), 0.3430 (3Q), 3.0821 (Max); Robust: –2.2605 (Min), –0.3488 (1Q), 0.0125 (Median), 0.3325 (3Q), 3.3593 (Max).

[b]Multiple R^2 (Linear): 0.3706, adjusted R^2: 0.3065; F-statistic: 5.782 on 11 and 108 DF; *P* value: 2.736e-07.

just 2 components with eigenvalues greater than unity. A varimax factor analysis (Table 3) to estimate the underlying factors showed that a number of the measures had uniquenesses in excess of .90. Five factors could be clearly and substantively identified as predictive indices. One unique (.972) test measure, Fib, showed some predictive value in the regression analysis and therefore was also retained though its relative contribution to the blood profile was too small to yield to factor extraction. In variance order, the independent underlying factors in the 11 blood tests can be described as cholesterol, fat, low HDL, IL-6, Lp -a, and Fib.

Table 4 shows the results of a standardized regression analysis predicting ischemic index from the factor scores. Changes in fat are first, followed by changes in cholesterol, in providing the greatest predictive value in estimating changes in ischemia.

The predicted values of this regression provide a single composite predictor. Regression of ischemic index on this composite blood profile is shown in Figure 3, standardized for equal scaling of predictor and predicted. The 95% confidence interval (green) for the regression coefficient is shown (0.47-0.70) and indicates the variance common to the 2 variables. Although this analysis assumes normal distribution, distribution-free estimates of the regression coefficients based on rank order (0.60; Kendall) and rank differences (0.58; Spearman) differ minimally from the normal least squares result (0.60). The range of coefficient estimates from different methods (0.57-0.60) is also displayed (yellow). That is, 3 independent methods yield essentially the same estimate of the proportion of underlying variance shared by predictors and predicted.

Discussion

Atherosclerotic CAD is a complex process involving both the deposition of fatty acids within the walls of the arteries[1,7-9,28] where they can be catabolized for energy under emergency conditions and an inflammatory response to the over accumulation of this material. This process is worsened when Hcy deposition occurs and complexes with LDL cholesterol to form Hcy thiolactone LDL cholesterol. Hence, the harmful effect of Hcy is dependent on it's interaction with LDL cholesterol.[29,30] Figure 4 shows the effect of VLDL catabolism to LDL cholesterol, which is then deposited within the walls of the coronary artery. This sets off a series of events, including

Table 3. Varimax Factor Analysis of Blood Chemistry Changes[a,b,c]

	Loadings					
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
TC	0.925	0.298		0.174	0.151	
LDL	0.962	0.133		0.165	0.129	
Low HDL	–0.154	–0.957	–0.152	–0.167		
TC.HDL	0.710	0.271	0.551	0.217	0.187	0.178
TG	0.257	0.904		0.184	0.263	
TG.HDL	0.207	0.778	0.475	0.202	0.230	0.164
CRP		0.281		0.105		
IL	0.153	0.210		0.950	0.136	
Hcy	0.217	0.204	0.178	0.426	0.295	
Fibrin		0.136		0.204		
Lp	0.232	0.217	0.216	0.250	0.886	

Note: TC, total cholesterol; LDL, low-density lipoprotein; HDL, high density lipoprotein; TG, triglycerides; CRP, C-reactive protein; IL, interleukin; Hcy, homocysteine; Lp, lipoprotein.
[a]Uniquenesses: 0.005 (TC), 0.005 (LDL), 0.005 (HDL), 0.005 (TC.HDL), 0.005 (TG), 0.005 (TG.HDL), 0.905 (CRP), 0.005 (IL), 0.610 (Hcy) 0.920 (Fibrin), 0.005 (Lp)
[b]SS loadings: 2.532 (Factor 1), 1.857 (Factor 2), 1.553 (Factor 3), 1.401 (Factor 4), 1.117 (Factor 5), 0.069 (Factor 6); Proportion Var: 0.230 (Factor 1), 0.169 (Factor 2), 0.141 (Factor 3), 0.127 (Factor 4), 0.102 (Factor 5), 0.006 (Factor 6); Cumulative Var: 0.230 (Factor 1), 0.399 (Factor 2), 0.540 (Factor 3), 0.668 (Factor 4), 0.769 (Factor 5), 0.775 (Factor 6).
[c]Test of the hypothesis that 6 factors are sufficient. The χ^2 statistic is 257.65 on 4 degrees of freedom. The *P* value is 1.46e-54.

Table 4. Regression of 1-Year Changes in Nuclear Image Determinations of the Coronary Blood Flow Ischemic Index on Blood Chemistry Profile Change Factors[a,f]

Coefficients	Estimate	*t* Value	Pr (>|*t*|)
Intercept	0	0	1.000[b]
Factor1 cholesterol	.276	3.648	0.000[c]
Factor2 fat	.329	4.315	0.000[c]
Factor3 low high density lipoprotein	.133	1.747	0.083[b]
Factor4 interleukin-6	.173	2.236	0.027[d]
Factor5 lipoprotein-a	.220	2.897	0.005[e]
Fibrinogen measure	.180	2.299	0.023[d]

[a]Residuals: –2.084051 (Min), –0.412194 (1Q), –0.001096 (Median), 0.400191 (3Q), 3.106253 (Max)
Significance codes: [b]0.1, [c]0.001, [d]0.05, [e]0.01.
[f]Residual standard error: 0.83 on 113 degrees of freedom; multiple R^2: 0.36, adjusted R^2: 0.32; F-statistic: 10.46 on 6 and 113 DF; *P* value: 3.333e-09.

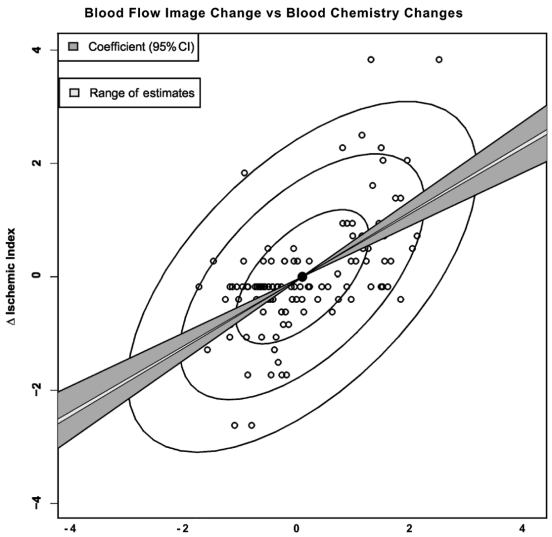

Figure 3. Standardized regression of coronary blood flow (nuclear imaged ischemic index) on composite blood profile (cholesterol, fat, HDL, IL-6, Lp-a, and Fib). The X-axis displays the composite blood profile including TC, fat, lowHDL, IL-6, Lp, and Fib. The Y-axis displays changes in ischemia as measured by nuclear imaging. The standard regression analysis shows both the range of estimates (yellow) and the 95% confidence intervals (green). HDL, high density lipoprotein; IL-6, interleukin-6; Lp-a, lipoprotein-a; Fib, fibrinogen; Tc, total cholesterol.

the vascular irritation and the release of IL-6. Interleukin-6 has multiple effects as shown in Figures 4 and 5. Like Hcy, IL-6 does not act alone but follows the process of vascular damage resulting from lipid deposits within the arterial walls. Compliance of coronary arterial walls is required to maximize the vasodilatory effect of coronary arteries following neuroendocrine[31,32] stimulation. As shown in Figure 6A, the ability to enhance CFR can and has been measured[33,34] and showed following pharmacologic stress with dipyridamole. This may be better understood by looking at Figure 6B, where the red lines show the effect of arterial wall vasodilation following dipyridamole. This vasodilation may be partially limited before any significant deposit of

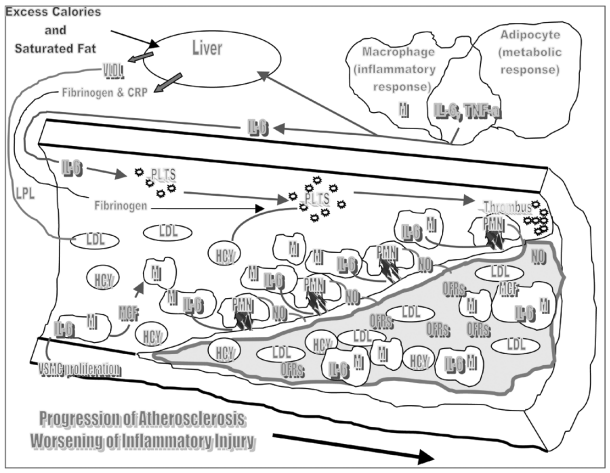

Figure 4. Inflammation producing vulnerable inflammatory plaques. Excess calories and saturated fat result in the production of the very low-density lipoprotein (VLDL) cholesterol by the liver, which is converted by lipoprotein lipase (LPL) in capillaries to low-density lipoprotein (LDL) cholesterol, which is deposited into the endothelium along with homocysteine (Hcy) helping to produce an inflammatory response leading to macrocyte accumulation. Both macrophages (M) and adipose tissue synthesize and release inteleukin-6 (IL-6) and tissue necrosis factor-alpha (TNF-α) that (a) results in increased production of acute phase reactants by the liver, which include Fib and C-reactive protein (CRP), (b) promotes vascular smooth muscle cell (VSMC) proliferation in the media, (c) stimulate adhesion (YY) molecules promoting polymorphonuclear leukocytes (PMNs) attachment to the endothelium and the subsequent production and release of metalloproteinases (MMPs) and monocyte chemotactic factor, which attracts more PMNs, and (d) promotes platelet aggregation and thrombus formation as shown.

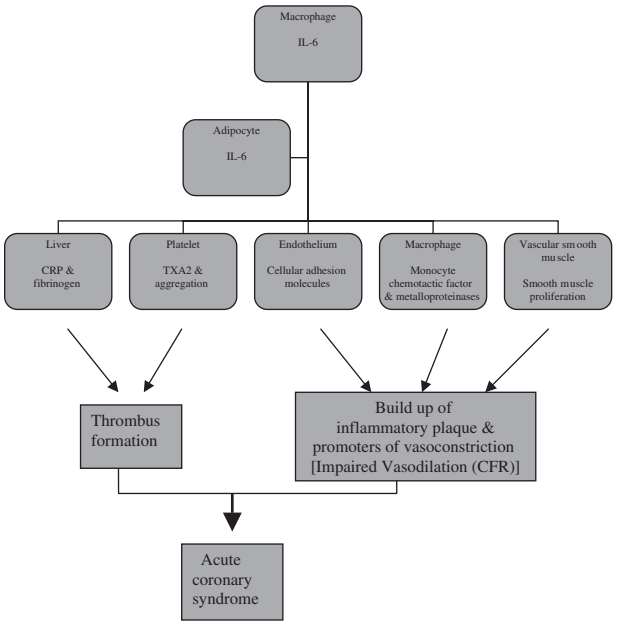

Figure 5. Interleukin-6 controls several components leading to coronary artery disease. Interleukin-6 (IL-6) production by both macrophages and adipose cells affect liver, platelet, endothelial, other macrophages, and vascular smooth muscle cells in different way, leading to thrombus formation and the build up of inflammation within the walls of the coronary arteries. The final result is either an ischemic state or complete occlusion of coronary blood flow followed by infarction, both of which are currently referred to as acute coronary syndromes (ACS).

lipid or fat and inflammatory material under conditions of vasomotor dysfunction or damage to the endothelium. As CAD progresses, the artery's flow reserve (CFR) is further reduced as a consequence of reduced compliance as shown by a reduction in the ability of arteries to vasodilate to meet cardiac demand. This reduction in CFR is shown in Figure 6B by a reduction in the divergence of resting (blue) and enhanced (red) vasodilation. In the absence of physical demands being placed on the heart, the ability to induce vasodilation through dipyridamole and then quantitatively measure the flow allows us to physiologically assess the ischemic index and flow reserve.

Using our previously described quantitative method[7,8] to measure regional blood flow differences using MPI following pharmacologic stress and sestamibi, we looked at baseline findings of MPI of 120 study subjects and compared the results with venous (lipids and inflammatory) markers of CAD. As shown in this study, the venous markers of CAD provide no predictive value with R^2 essentially equal to zero. This means that these tests do not offer a diagnostic tool from which one cannot infer the extent of coronary artery ischemia. At first glance, this might appear unlikely until one recognizes that 50% of all people experiencing a myocardial infarction have TC levels of 150 mg/dL or less, with 70% to 85% of all infarctions occurring in arteries with <30% luminal diameter narrowing, making the role of physiologic SPECT imaging extremely important in determining the extent of early CAD.

We further looked at changes in blood chemistry factors and were able to identify 5 factors and 1 measure (cholesterol, fat, lowHDL, Lp -a, IL-6, Fib), which were found to provide prognostic value in revealing changes in ischemia. These factors share about 60% of their variance with the ischemic index. The largest shared component is the fat factor. Although this is statistically significant, it also point out that venous markers of CAD cannot completely predict changes in coronary blood flow as measured by MPI.

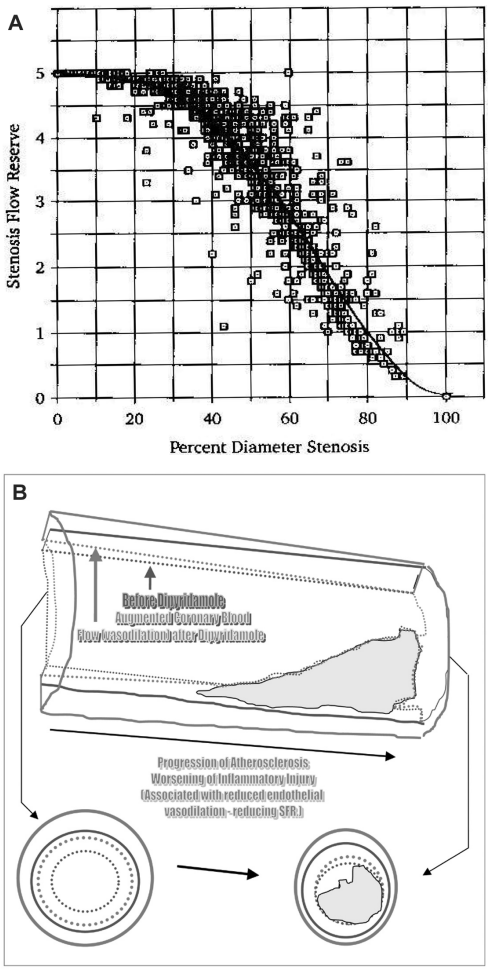

Figure 6. A, Changes in CFR following intravenous dipyridamole vasodilation. (This is for the discussion section.) Seventy to 85% of the nutrients flowing through the coronary arteries are extracted for resting myocardial metabolic needs. The coronary arteries are able to vasodilate to increase coronary blood flow by a factor of 5 to 6 times resting flow. This CFR is not dependent on the buildup of vulnerable inflammatory plaque and normal endothelial function. When vulnerable inflammatory plaque production begins, there is initial distention of the vessel wall outwards followed by the inward intrusion on the coronary lumen, resulting in angiographically detectable coronary artery stenosis. This process results in a reduction in CFR. For measuring CFR, assessment of physiologic function of the artery is required, which can be measured quantitatively by inducing and measuring changes in CFR. B, Dipyridamole induction of CFR. In this figure, dashed lines indicate the endothelial wall of the artery, whereas solid lines represent the adventitia. During the resting state, the artery carries the least amount of blood and is shown in blue. Following vasodilatation by dipyridamole, which increases the CFR, the artery is shown in red. Note that in regions of normal (left) endothelial function and absence of inflammatory plaque, the artery is able to maximally dilate for a CFR of 5.0, whereas in areas of vulnerable inflammatory plaques where the endothelium is also dysfunctional, the CFR is not increased from baseline, and when compared with the expected flow through an artery without stenosis, it is actually less than 1.0. CFR indicates coronary flow reserve.

Conclusion

Measurement of multiple risk factors for CAD, including measures of lipids and inflammatory markers of CAD, do not provide diagnostic information, which can be used to calculate or predict coronary blood flow as measured by MPI.[35-40] The ability of a coronary artery to dilate and subsequently enhance regional coronary blood flow to meet the cardiac demands may be influenced by these risk factors, but CFR is dependent on the ability of the arteries to respond to cardiac demands, including endothelial integrity and responsivity, arterial compliance, the buildup of inflammatory material within the walls of an artery, and other factors that can only be measured directly and quantified as we and others have shown, using MPI. Without prior knowledge of coronary flow, these venous markers do not provide a mechanism for predicting the actual severity of CAD.

Changes in risk factors, with or without treatment, provide limited predictability in changes in myocardial blood flow. The majority of this predictability lies in the measurement of lipids with little additional information provided by the measurement of inflammatory markers, which are correlated with changes in lipids. In other words, with changes in lipids, there will be an associated change in inflammatory markers so that the additional measurement of these inflammatory markers adds little additional prognostic information for predicting the expected changes in coronary blood flow as measured by MPI. It is important to emphasize that direct measurement of coronary blood flow is required to initially determine coronary ischemia, whereas changes (not absolute determination) in coronary ischemia can be partially predicted based on changes in (in order of magnitude of effect) fat, cholesterol, Lp -a, Fib, IL-6, and lowHDL. These variables do not account for changes in vasomotor tone, endothelial function, and/or other as of yet unknown factors that influence coronary flow reserve. Nuclear imaging can provide diagnostic information on the status of coronary blood flow. Blood chemistry profiles cannot, but monitoring changes in blood chemistry profile can, offer diagnostic clues to concurrent changes in myocardial blood flow.

References

1. Fleming RM. Coronary artery disease is more than just coronary lumen disease. *Am J Cardiol*. 2001;88:599-600.
2. Fleming RM, Kirkeeide RL, Taegtmeyer H, Adyanthaya A, Cassidy DB, Goldstein RA. A comparison of technetium

99-m teboroxime tomography to automated quantitative coronary arteriography and thallium-201 SPECT. *J Am Coll. Cardiol*. 1991;17:1297-1302.
3. Masood Y, Liu YH, Depuey G, et al. Clinical validation of SPECT attenuation correction using x-ray computed tomography-derived attenuation maps: multicenter clinical trial with angiographic correlation. *J Nucl Cardiol*. 2005;12:676-686.
4. De Lorenzo A, Hachamovitch R, Kang X, et al. Prognostic value of myocardial perfusion SPECT versus exercise electrocardiography in patients with ST-segment depression on resting electrocardiography. *J Nucl Cardiol*. 2005;12:655-661.
5. Fleming RM, Gibbs HR, Swafford J. Using quantitative coronary arteriography to redefine SPECT sensitivity and specificity. *Am J Physiol Imaging*. 1992;7:59-65.
6. Fleming RM. Detecting coronary artery disease using SPECT imaging: a comparison of thallium-201 and teboroxime. *Am J Physiol Imaging*. 1992;7:20-23.
7. Fleming RM, Boyd L, Forster M. Angina is caused by regional blood flow differences—proof of a physiologic (not anatomic) narrowing. Joint Session of the European Society of Cardiology and the American College of Cardiology, Annual American College of Cardiology Scientific Sessions 49th; March 2000; Anaheim, CA. www.prous.com for physician training and CME credit, Accessed April 2000.
8. Fleming RM. Angina and coronary ischemia are the result of coronary regional blood flow differences. *J Am Coll Angiol*. 2003;1:127-142.
9. Fleming RM.: Chapter 64. *The Pathogenesis of Vascular Disease*. *Textbook of Angiology.* John C. Chang Editor, Springer-Verlag New York, NY. 1999, pp. 787-798.
10. Koh KK, Han SH, Quon MJ. Inflammatory markers and the metabolic syndrome: insights from therapeutic interventions. *J Am Coll Cardiol*. 2005;46:1978-1985.
11. Lubbock LA, Goh A, Ali S, Ritchie J, Whooley MA. Relation of low socioeconomic status to C-reactive protein in patients with coronary heart disease (from the heart and soul study). *Am J Cardiol*. 2005;96:1506-1511.
12. Robinson SD, Dawson P, Ludlam CA, Boon NA, Newby DE. Vascular and fibrinolytic effects of intra-arterial tumor necrosis factor-alpha in patients with coronary heart disease. *Clin Sci*. 2006;110:353-360.
13. Ginsburg D. Genetic risk factors for arterial thrombosis and inflammation. *Hematology*. 2005:442-444.
14. Fleming RM. The Fleming unified theory of vascular disease: A link between atherosclerosis, inflammation, and bacterially aggravated atherosclerosis (BAA). *Angiology*. 2000;51:87-89.
15. Fleming RM. The clinical importance of risk factor modification: looking at both myocardial viability (MV) and myocardial perfusion imaging (MPI). *Int J Angiol*. 2000;9:55-69.
16. Fleming RM. Using C-reactive protein as a marker of bacterially aggravated atherosclerosis in acute coronary syndromes. *J Amer Coll Angiol*. 2003;1:165-171.
17. Kantarci A, Van Dyke TE. Resolution of inflammation in periodontitis. *J Periodontol*. 2005;76:2168-2174.
18. Liao JK. Clinical implications for statin pleiotropy. *Curr Opin Lipidol*. 2005;16:624-629.
19. Sie MP, Sayed-Tabatabei FA, Oei HH, et al. Interleukin 6-174 G/C promoter polymorphism and risk of coronary heart disease. Results from the Rotterdam study and a meta-analysis. *Arterioscler Thromb Vasc Biol*. 2006;26:212-217.
20. Fleming RM. The effect of high, moderate, and low fat diets on weight loss and cardiovascular disease risk factors. *Prev Cardiol*. 2002;V(III):110-118.
21. Fleming RM, Ketchum K, Fleming DM, Gaede R. Treating hyperlipidemia in the elderly. *Angiology*. 1995;46:1075-1083.
22. Fleming RM, Ketchum K, Fleming DM, Gaede R. Assessing the independent effect of dietary counseling and hypolipidemic medications on serum lipids. *Angiology*. 1996;47:831-840.
23. Fleming RM, Rose CH, Feldmann KM. Comparing a high dose dipyridamole SPECT imaging protocol with dobutamine and exercise stress testing protocols. *Angiology*. 1995;46:547-556
24. Fleming RM, Feldmann KM, Fleming DM. Comparing a high dose dipyridamole SPECT imaging protocol with dobutamine and exercise stress testing protocols. Part II: using high-dose dipyridamole to determine lung-to-heart ratios. *Int J Angiol*. 1998;7:325-328.
25. Fleming RM, Feldmann KM, Fleming DM. Comparing a high dose dipyridamole SPECT imaging protocol with dobutamine and exercise stress testing protocols. Part III: using dobutamine to determine lung-to-heart ratios, left ventricular dysfunction and a potential viability marker. *Int J of Angiol*. 1999;8:22-26.
26. Fleming RM. High-dose dipyridamole and gated sestamibi SPECT imaging provide diagnostic resting and stress ejection fractions useful for predicting the extent of coronary artery disease. *Angiology*. 2002;53:415-421.
27. Fleming RM. A tate-en-tate comparison of ejection fraction and regional wall motion abnormalities as measured by echocardiography and gated sestamibi SPECT. *Angiology*. 2002;53:313-321.
28. Fleming RM, Boyd L, Forster M. Reversing heart disease in the new millennium—the Fleming unified theory. *Angiology*. 2000;51:617-629.
29. Salahuddin MI, Ahmed SI. Homocysteine level in patients with established transmural myocardial infarction. *J Coll Physicians Surg Pak*. 2005;15:520-523.
30. Moron deSalim AR, Garces Pasamontes A. Effect of the supplementation of vitamins B12, B6 and folic acid on homocysteine and plasmatic lipids in patients with hyperlipoproteinemic secondary type IV. *Arch Latinoam Nutr*. 2005;55:28-33.
31. Juttler E, Tarabin V, Schwaniger M. Interleukin-6: a possible neuromodulator induced by neuronal activity. *Neuroscientist*. 2002;8:268-275.
32. Hamaad A, Sosin M, Blann AD, Patel J, Lip GYH, MacFadyen RJ. Markers of inflammation in acute coronary

syndromes: association with increased heart rate and reductions in heart rate variability. *Clin Cardiol*. 2005;28:570-576.
33. Fleming RM, Harrington GM. Quantitative coronary arteriography and it's assessment of atherosclerosis. Part 1. Examining the independent variables. *Angiology*. 1994; 45:829-833.
34. Fleming RM, Harrington GM. Quantitative coronary arteriography and it's assessment of atherosclerosis. Part 2. Calculating stenosis flow reserve directly from percent diameter stenosis. *Angiology*. 1994;45:835-840.
35. Michelena HI, VanDecker WA. Radionuclide-based insights into the pathophysiology of ischemic heart disease: beyond diagnosis. *J Investig Med*. 2005;53:176-191.
36. Bulow H, Schwaiger M. Nuclear cardiology in acute coronary syndromes. *Q J Nucl Med Mol Imaging*. 2005;49:59-71.
37. Clark AN, Beller GA. The present role of nuclear cardiology in clinical practice. *Q J Nucl Mol Imaging*. 2005;49:43-58.
38. Cuocolo A, Acampa W, Imbriaco M, De Luca N, Iovino GL, Salvatore M. The many ways to myocardial perfusion imaging. *Q J Nucl Mol Imaging*. 2005;49:4-18.
39. Paul AK, Nabi HA. Gated myocardial perfusion SPECT: basic principles, technical aspects, and clinical applications. *J Nucl Med Technol*. 2004;32:179-187.
40. Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. *J Am Coll Cardiol*. 2004;44: 1533-1542.