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Reversing Heart Disease in the New Millennium

The Fleming Unified Theory

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ABSTRACT

Nineteen people without prior history of documented heart disease were studied for 8 months to determine the effect of treatment based on an immunologic unified theory of vascular disease. Subjects underwent myocardial perfusion imaging to quantify the extent and severity of coronary artery disease, along with assessment of wall motion abnormalities and ejection fraction by both nuclear and echocardiographic methods. These tests were repeated at the end of the study. Treatment consisted of dietary changes, treatment of cholesterol, triglycerides, homocysteine, lipoprotein (a), fibrinogen, C-reactive protein, and infection. Patients who followed the dietary recommendations demonstrated statistically reduced disease in all three major coronary arteries, whereas those individuals who followed high-protein diets demonstrated statistically greater levels of disease.

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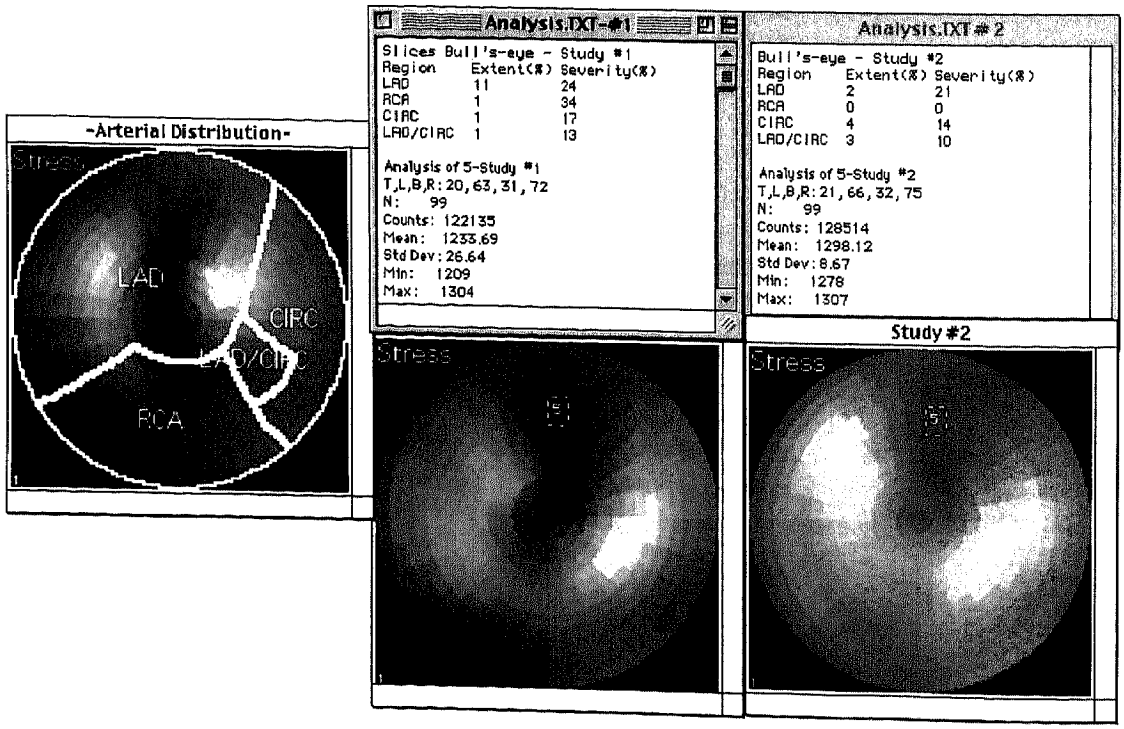
Introduction

Attempts at controlling or reversing coronary artery disease have resulted in mixed results despite efforts by countless investigators over the past 50 years. Recently published data[1] derived from positron emission tomography (PET) imaging have shown that risk factor modification with extreme dietary (vegetarian) and life-style changes may result in regression of coronary artery disease in one third of the cases, with stabilization in one third, and progression of disease in the remaining one third of individuals studied. These changes are equivalent to chance outcomes and resulted in both the recognition for and development of an immunologic unified theory of vascular disease[2] first presented in 1997.

The basis for this unified theory was failure of individual approaches to successfully treat coronary artery disease and the recognition of multiple contributions from various disciplines not previously connected. The acceptance of these contributions[3-65] that initially appeared to be disconnected, rather than rejection of some or all of them, led to the development of an immunologic unifying theory, which explained why each of the previous approaches had validity with partial beneficial effect on the treatment of heart disease without complete success. While the theory describes the relationship among eight independent groups of factors, all of which appear to be involved to varying degrees in different individuals, it has not yet been tested in the clinical setting.

In order to test this theory and determine the independent effect of each of these variables we

Figure 1. Example of nuclear study with arterial distributions. Arterial distribution from myocardial perfusion imaging is divided as shown in the "arterial distribution" image at the far left with LAD representing the left anterior descending artery distribution, RCA representing the right coronary artery, CIRC is the left circumflex (LCx) distribution and LAD/CIRC (L-C) representing the watershed region between the LAD and LCx arteries. The next two images represent "bullseye" images of the maximal coronary flow acquired during the patients' first and second study. Immediately above each image is the quantitation of extent and severity of flow in each of the vascular distributions. For example, the second study shows 2% (extent) of the LAD involved with 21% severity compared to the initial study, where 24% severity was noted over 11% of the LAD distribution.



prospectively studied 19 individuals without a history of documented coronary artery disease (primary prevention) over an 8-month period and asked the following preliminary questions. First, what effect is seen with treatment of each of the independent groups of factors? Second, can a statistical regression in extent and severity of coronary artery disease be documented as a result of treatment? Third, is there a relationship between these independent variables and changes in coronary blood flow? Finally, does an individually designed program based on treatment of these independent variables, patient myocardial perfusion imaging (MPI), and echocardiographic findings result in any difference in outcome compared with previous work currently published in the medical literature?

Methods

Patient Recruitment

Nineteen people without a prior history of documented coronary artery disease were enrolled in a prospective study to compare the results of changes in MPI, wall motion, weight, and nine independent blood work variables over an 8-month period. Patients were excluded from the study if they had undergone any prior coronary revascularization procedure (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, etc) or if they had a history of known heart disease. Patients were excluded if they had "severe" aortic stenosis, were pregnant, or planned to become pregnant. All patients signed institutional consent forms before participation in the study.

Echocardiographic Evaluation

Conventional 2D, M-mode, and Doppler (including color flow) echocardiographic evaluation was performed using standard views consisting of parasternal long- and short-axis views, apical two-, four-, and five-chamber views as well as subxiphoid views. These studies were performed at the beginning and end of the study to look for evidence of regional wall motion abnormalities including diastolic dysfunction.

Myocardial Perfusion Imaging (MPI)

Gated single photon emission computed tomography (Gated SPECT) imaging with high-dose dipyridamole (HDD) and sestamibi was used to look for coronary artery disease as previously[1,66-71] described. Patients underwent imaging at the beginning and end of the study. The extent and severity of perfusion through each of the coronary beds was quantified as shown in Figure 1. Differences between the initial and follow-up evaluation were recorded for each patient as changes in the extent of disease in the left anterior descending (LAD), right coronary artery (RCA), left circumflex (LCx), and the watershed area of the LAD-LCx (L-C) as noted in Figure 1.

Venous Blood Samples (Independent Variables)

All blood work was accomplished in the fasting state with patients having venous blood samples obtained before 8:30 AM. Samples were taken for homocysteine, lipoprotein (a) [Lp(a)], fibrinogen, C-reactive protein (C-RP), triglycerides (Trigs), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and very-low-density lipoprotein (VLDL) cholesterol. When C-RP levels were elevated, acute-phase antibodies (IgM) were drawn to determine if an acute bacterial infection resulting from *H. pylori, C. pneumoniae, or S. pneumoniae* was the cause of the elevated C-RP versus an inflammatory process unrelated to bacterial infection. Blood work was compared at the beginning and end of the study.

Treatment of Blood Work Results

Owing to differences between independent variables a single prescription for medical management of an abnormal value could not be made without flexibility. Table I shows the treatment guidelines followed from beginning to end of the study in an effort to maximize the benefit from each medication while minimizing the number of medications used in an effort to enhance patient adherence to medical regimen and provide a future model to limit medical costs. For example, a patient with elevated triglycerides, fibrinogen, and lipoprotein (a) received fenofibrate, whereas a patient with only elevated lipoprotein (a) would receive Lovastatin®. The acceptable levels in this

Table I

Treatment Protocol Based on Independent Variables

Independent Variables (Acceptable Levels)	Dietary (Calories and Saturated Fats)	Folate, Vitamins B6 and B12	Statins	Fenofibrate	Interleukin Inhibitors	Clarithromycin (500 mg bid × 14 Days)
LDL (<100 mg/dL)	X		X	+/-		
TG (<150 mg/dL)	X		+/-	X		
Fibrinogen (200–400 mg/dL)				X		
Lp(a) (<30 mg/dL)			Lovastatin®	X		
Homocysteine (<9.0 μmole/L)	X	X				
Pos CRP (≤0.9 mg/dL) and Neg Abs			Pravastatin®, Fluvastatin®		X	+/-
Pos CRP (>0.9 mg/dL) and Pos Abs					+/-	X

LDL = low-density lipoprotein cholesterol, TG = triglycerides, Lp(a) = lipoprotein (a), Pos CRP = elevated C-reactive protein, Neg Abs = negative acute-phase antibodies, Pos Abs = positive acute-phase antibodies.

study for each of these independent factors are shown in Table I. Treatment was initiated when an independent variable was considered elevated by these standards.

Dietary Recommendations

Caloric determination was made for each of the patients in the study by using either caloric estimation of 10 kCal/pound per day or actual caloric determination using the CardioO2 system from Medical Graphics Corporation. Once the actual number of calories was determined, a recommendation was made for each patient regarding daily intake.[72] This intake consisted of 15% of their daily calories in protein, 70% carbohydrate (including complex carbohydrates), and 15% in fat with a 2:1 ratio of nonsaturated (polyunsaturated, monosaturated) to saturated fat intake. Of the 19 individuals originally enrolled in our study, 16 reported they followed these dietary guidelines, while three decided to follow a popular high-protein diet. Those following our recommended dietary guidelines represented the treatment group (TxG), while those following the high-protein (HPG) diet were considered an independent group. Except for these dietary differences, the two groups were treated identically.

Other Standards of Care Treatment

Patients with anginal symptoms were treated with standard drug regimens including the use of long-acting nitroglycerine (Imdur, Ismo), slow calcium channel antagonists (Procardia XL®, diltiazem), and β-blockers (tenormin, atenolol) medications. None of the patients were taking medications that would have increased the independent variables.

Statistical Analysis

Descriptive statistics were determined including the mean ± standard deviation for each of the independent variables, in addition to weight and age of patients. Following determination of the extent and severity of coronary artery disease by MPI, the percent of involvement was determined for each individual along with changes from beginning to the end of the study. These results were then averaged with percent change ± standard deviation. Differences between groups were

determined by using unmatched two-tailed t tests. Each of the independent variables was further analyzed to determine any correlational relationships between the independent variables and change in extent or severity of disease and changes in wall motion.

Results

There were eight women and eight men in the TxG with an average age of 48 ±10 years compared with an average age of 56 ±13 years in the HPG. The TxG consisted of 12 Caucasians, two African-Americans, one Hispanic, and one Italian immigrant. The HPG consisted of two men and one woman—all Caucasian.

The average results for each of the independent variables along with percent changes for each group are shown in Table II. Despite differences in dietary habits, over the 8-month period of time there were no statistically significant differences in independent variables between the two groups except for Lp(a). However, the TxG demonstrated gradual consistent improvement in each of the independent variables while the HPG demonstrated consistent worsening of these same independent variables. While no single variable was statistically significant, the cumulative effects were. Subjects in the TxG showed a slight increase in weight (2.2%) over the duration of the study, while patients following the high-protein diet lost an average of 0.17% of their body weight, but as a group the HPG individuals weighed more than those in the TxG.

There was a reduction in homocysteine levels in the TxG by 2.8% while patients eating more protein showed an actual increase in homocysteine levels by 3.0%. These differences were not statistically significant. Despite treatment, both groups demonstrated an increase in lipoprotein (a) levels with greater increases seen in the HPG. C-reactive protein (C-RP) demonstrated a significant drop in the TxG but an increase in the HPG. Of the five people in the TxG with elevated C-RP levels, four of 16 (25%) had acute-phase antibodies, including two to *H. pylori,* one to *C. pneu-*

Table II

Independent Variable Changes by Group

Independent Variable	Treatment Group Initial Values	Treatment Group Final Values	Percent Change in Treatment Group	High-Protein Group Initial Values	High-Protein Group Final Values	Percent Change in High-Protein Group
Weight	178.7	182.7	+2.2	194.7	194.3	-0.2
Homocysteine	8.9	8.7	-2.8	6.9	9.0	+3.0
Lipoprotein (a)	47.5	57.6	+21.2	5.0	10.5	+110.0
C-reactive protein	0.9	0.4	-52.1	3.0	1.2	+61.0
Triglycerides	215.2	246.7	-38.8	108.5	169.3	+56.0
Total cholesterol	222.6	188.6	-15.3	132.5	156.7	+18.2
HDL cholesterol	50.6	46.5	-8.0	50.0	45.7	-9.6
LDL cholesterol	132.8	117.3	-11.7	60.5	77.3	+27.8
VLDL cholesterol	39.2	24.8	-36.8	21.5	33.7	+56.6
Fibrinogen	371.1	347.9	-6.2	292.0	329.5	+12.8

moniae, and one to both *H. pylori* and *C. pneumoniae*. The fifth person had ulcerative colitis (UC), which demonstrated a normalization of C-RP following acute treatment for UC.

Triglyceride levels demonstrated a 38.8% reduction in the TxG while a 56% increase was noted in the HPG. This was associated with concomitant changes in VLDL cholesterol levels as shown in Table II. The total cholesterol levels decreased by 15.3% in the TxG and increased by 18.2% in the HPG. The increase in TC in the HPG was secondary to increases in both triglycerides and LDL. The LDL levels decreased in the TxG by 11.7% while increasing by 27.8% in the HPG. The fibrinogen level in the TxG also showed a reduction (6.2%), while the HPG showed an increase of 12.8 percent.

The effect of each of these independent variables in the TxG are shown in Figure 2. Except for the Lp(a) group, each of the independent variables demonstrated improvement with treatment. The most striking improvement was seen in the triglyceride levels, which approached, but did not reach, statistical significance. Despite improvement in the TxG and worsening of independent variables in the HPG, the differences in these independent variables approached, but did not reach, statistical significance. No single independent variable had more than a moderate (0.70) correlation with outcomes as measured by extent or severity of disease, further emphasizing the need to treat all, and not just some, of the independent variables when one is trying to treat heart (vascular) disease.

Changes in the extent and severity of coronary artery disease are shown in Table III for both groups. In each of the four myocardial distributions (Figure 1), both the extent and severity of coronary artery disease demonstrated regression in the treatment group with the greatest effect

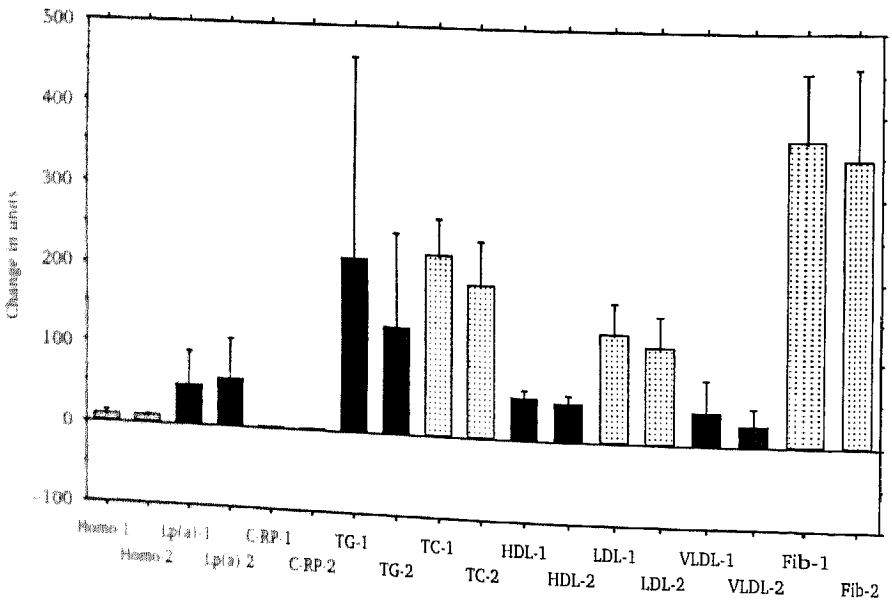


Figure 2. Treatment (TxG) group changes in independent variables. Each of the independent variables is represented by a bar graph showing the mean ± standard deviation for the results obtained before (1) and following (2) treatment For example, Homo-1 is the average homocysteine level (± standard deviation) before treatment and Homo-2 is the average homocysteine level (± standard deviation) following treatment. Also represented are Lp(a) [lipoprotein (a)], C-RP (C-reactive protein), TG (triglycerides), TC (total cholesterol), HDL (high-density lipoprotein cholesterol), LDL (low-density lipoprotein cholesterol), VLDL (very low-density lipoprotein cholesterol), and Fib (fibrinogen).

Table III

Changes in Extent and Severity of Disease

	Percent Extent LAD	Percent Severity LAD	Percent Extent RCA	Percent Severity RCA	Percent Extent LCx	Percent Severity LCx	Percent Extent L-C	Percent Severity L-C	Percent Extent Total	Percent Severity Total
TxG	-4.7	-5.0	-6.1	-10.3	-6.9	-8.2	-5.2	-3.2	-22.9	-21.8
HPG	+1.4	+7.0	+4.4	+17.9	+14.7	+11.8	+17.9	+13.4	+38.4	+50.1
p Value	<0.20	<0.005	<0.005	<0.001	<0.001	<0.001	<0.001	<0.005	<0.001	<0.001

TxG = treatment group, HPG = high-protein group, p Value = level of statistical significance between groups.

seen in the right coronary and left circumflex distributions. The extent and severity of disease in the LAD showed an average regression of 4.7 ±6.3% and 5.0 ±6.0%, respectively, compared with a progression of 1.4 ±10.8% (extent) and 7.0 ±5.2% (severity) in the HPG. The difference approached significance for extent of disease and was statistically significant ($p < 0.005$) for the severity of disease.

As shown in Table III and Figure 3, there was regression in both the extent and severity of disease for the RCA, LCx, and L-C distributions, which are statistically significantly ($p < 0.005$) different from the outcomes seen in the HPG. The cumulative effect in the TxG was a 22.9% regression in the extent of disease and a 21.8% reduction in the severity of disease, which was statistically significantly ($p < 0.001$) different from the advancement of disease seen in the HPG.

Regional wall motion abnormalities[70-71] were noted in seven (43.75%) of the 16 patients in the TxG, including four instances of anterior/anteroseptal (LAD) wall motion abnormality, four cases of inferior (RCA) wall motion abnormality, and two cases of anterolateral (LCx) wall motion abnormality. Of these, five of the individuals had wall motion abnormalities in only one region, one had wall motion abnormalities in two regions, and the last person had wall motion abnormalities in three myocardial regions. In each case, there was improvement in wall motion following treatment, which matched improvement in MPI in areas with non-Q wave myocardial infarction.

Discussion

Most studies have provided little useful information regarding women and minorities. This preliminary primary prevention study, while relatively small, not only demonstrated statistically significant outcomes based on treatment focusing on multiple independent variables but also studied essentially equal numbers of men and women, with approximately 20% minority participants. These 19 people were studied for an 8-month period to determine the potential benefit of individually treating patients based on an immunologically mediated theory of vascular disease. Based on the theory itself,[2] the overall benefit is dependent on the treatment of all abnormal independent variables and not just one or two of these. If this is correct, then no single independent variable[1] could account for differences seen in either myocardial blood flow or wall motion (viability) recovery. As in the real world and despite our best efforts, patients within the study subgrouped themselves unintentionally with three individuals deciding to go on a high-protein diet for varying periods of time during these 8 months.

Despite fluctuations in weight, minimal change was actually noted over the duration of the 8-month study. This is true of most "diets" where individuals initially show weight loss due to decreased caloric consumption and water loss. Over the course of time, extreme dietary regimens frequently result in initial weight loss fol-

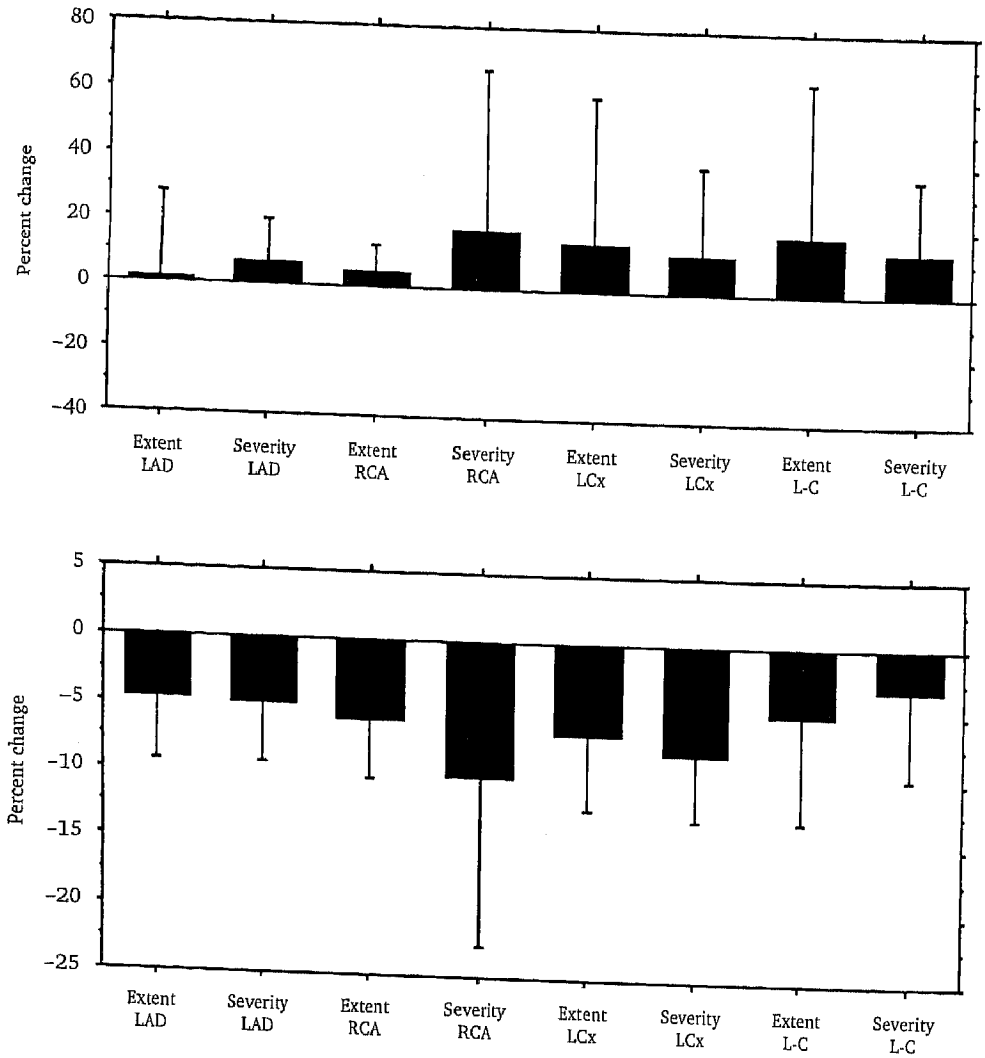


Figure 3. Changes in extent and severity of disease in HPG and TG. The upper panel reflects changes in the extent and severity of disease in the HPG for each of the four arterial distributions shown in Figure 1. These results are the average ± standard deviation changes. The average increase in extent and severity of disease ranged from 1.4 to 17.9 percent increase in coronary artery disease. The bottom panel demonstrates the same results for the treatment group with regression of disease ranging from 3.2 to 10.3 percent over the course of the study.

lowed by weight gain, increased triglycerides levels, and eventual progression[1] of intimal thickening, increased coronary artery disease, and decreased myocardial perfusion. Changes in weight in this study were identical to those previously reported[6,7] without any notable correlation to either the extent or severity of heart disease present or to the independent risk factors for heart disease themselves. This simple observation may help in part to understand why some slender people may have heart disease and some overweight individuals may not develop significant heart disease. It is also true that individuals in the TxG reported their clothing fitting more loosely without losing weight, suggesting that their body weight shifted from adipose tissue to

muscle mass. Clearly there are multiple factors involved and being overweight is not cardioprotective. Fluctuations in weight with high protein diets have also been reported previously[73] but frequently go unmentioned.

Following a balanced dietary regimen and medical treatment, individuals in the TxG showed improvement in their homocysteine levels. Those consuming a high-protein diet showed an increase in homocysteine levels reflecting an increased dietary loading of protein (methionine) and possible increased physiologic stress adversely affecting the body's attempt to handle the increased oxidative load. This in and of itself could lead to worsening of heart disease. When coupled with significantly increased Lp(a) levels, these individuals (HPG) may be at increased risk for vasoconstriction, thrombotic events, and subsequent myocardial infarction.

Individuals in the TxG also demonstrated reductions in serum triglycerides, LDL, TC, VLDL, HDL, and fibrinogen levels. None of these factors in and of themselves statistically accounted for improvement in coronary blood flow and recovered myocardial function. These changes are consistent with those changes we have reported,[6-7] previously. Individuals consuming high-protein diets received the same medications as participants in the TxG did. Despite this, increases in serum lipids were noted and were consistent with changes previously[73] reported for 24 individuals studied in the late 1970s. These results[6,7,73] would suggest that even though the numbers of individuals in the current study were small, they are representative of larger studies we and others have published and have the statistical significance in outcomes demonstrative of consequence. The earlier studies did not have the additional benefit of looking at myocardial blood flow or wall motion as this study did.

Of extreme interest was the treatment effect noted in individuals with elevated C-RP levels. C-reactive protein elevations are indicative of either an inflammatory or infectious process as previously discussed. The ability to distinguish between inflammatory versus infectious processes in this study was achieved by assessing the acute-phase antibody levels to three different bacteria proposed by researchers as possible causes of bacterially aggravated atherosclerosis (BAA).[74] MPI studies performed immediately after treatment with antibiotic therapy demonstrated improvement in coronary blood flow in all of the individuals so treated, with continued improvement documented on follow-up studies after completion of treatment.

While Lp(a) increased, improvement was seen once Lovastatin levels were increased to 40 mg with the evening meal and supports the need for higher dosing in an effort to reduce this variable, which will undoubtedly enhance the regression of atherosclerosis.

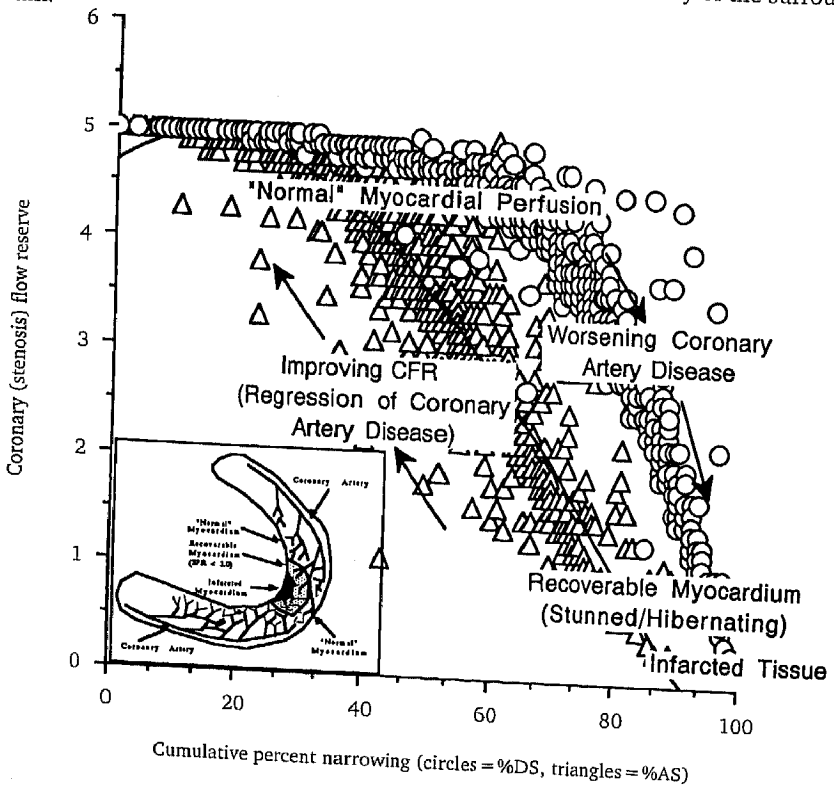
Reduction in both the extent and severity of coronary blood flow (5–10%) in the TxG demonstrated statistical improvement during the 8-month study while the HPG showed statistical worsening of disease. Clearly, 8 months represents adequate time for regression or progression[61] of disease. The improvement does not appear to be due to any one independent variable but due rather to improvement in multiple variables. Statistical reduction in extent and severity of coronary blood flow was also associated with improvement in myocardial function (viability).

Conclusion

Reduction in the extent and severity of myocardial perfusion would be expected to have its greatest effect on the smaller and medium-sized blood vessels since changes of equal effect would be more pronounced in smaller blood vessels. These arteries are not evaluated by conventional angiography. Ischemic phenomena would affect the endocardial region first, which is farthest downstream from arterial blood flow. These areas are documented by non-Q wave myocardial infarction on MPI and regional wall motion abnormalities on either nuclear or echocardiographic imaging.

Following myocardial infarction there is a region of permanent myocardial damage surrounded by "stunned/hibernating/recoverable" (SHR) myocardium (Figure 4), which is further surrounded by "normal" myocardium. The SHR myocardium represents a region where sufficient reduction in blood flow has occurred to inhibit the function of myocytes but not to result in permanent damage unless further deterioration in blood flow occurs. On the assumption that reversal of atherosclerosis would benefit the smaller blood vessels first, then these regions should demon-

Figure 4. Recovery of viable but stunned myocardium. Stenosis flow reserve (the ability to increase blood flow to the heart with increased demand) and its relationship to percent diameter and area stenosis[29,30,77] are shown in this figure. When coronary flow is diminished from atherosclerosis, the coronary arteries are limited by their ability to increase blood flow upon demand/need. In regions with severely diseased arteries myocardial damage occurs (infarction) with surrounding regions having less flow than normal but greater than the infarcted region. These areas are nonfunctional but viable. When studied by nuclear or echocardiographic studies they appear hypokinetic. These same regions would normally progress to complete cell death, but with regression of atherosclerosis and improved coronary flow, they move from the region of "stunned/hibernating/recoverable" myocardium to recovered myocardium resulting in function and regional wall motion. The infarcted tissue remains infarcted with recovery of the surrounding myocardium.



strate improved blood flow and recovery of myocardium as seen on MPI and echocardiography in this study.

As discovered in this study, seven individuals in the TxG had regional wall motion abnormalities on both nuclear and echocardiographic evaluations. These regions represented sites of non-Q wave infarction as documented by rest image abnormalities during resting sestamibi studies and normal-appearing electrocardiograms. Repeat sestamibi imaging demonstrated reduced size in SHR myocardium with reductions in the size of decreased tracer uptake at rest, showing recovery of SHR myocardium. These sites matched recovery of wall motion on both gated SPECT sestamibi and echocardiographic evaluations. The truly infarcted tissue does not recover, but SHR myocardium can clearly be rescued once sufficiently improved blood flow is achieved, allowing the myocytes to once again become functional. The usual conventional approach results in progression of heart disease, transforming non-Q wave MIs into Q wave MIs (detectable with ECG and auscultation) and subsequent[75-76] long-term "heart failure."

Despite prior efforts to find a single factor (dietary cholesterol, bacterial infection, etc), which can be treated, atherosclerotic disease is increas-

ing. The results of this novel approach to treating atherosclerotic coronary artery disease (CAD) based on an immunologically mediated disease model, precipitated by poor dietary habits (saturated fat and excess calories) and lifestyle choices, demonstrated not only the ability to regress the extent and severity of disease but also the recovery of SHR myocardium, which would reduce CHF symptoms, morbidity, and mortality. These dietary habits and lifestyle choices result in damaged endothelium with subsequent development of plaques, which the body's immunologic system appears to attempt to control or minimize. The process can, however, be perturbed by individual variables, eg, fibrinogen (genetic, iatrogenic); homocysteine (increased stress, poor vitamin or mineral intake, increased dietary load of protein); lipoprotein (a), which appears to be mostly genetic; C-reactive protein (from inflammatory or infectious damage to the artery); or a combination of these and other factors.[2] Efforts to control or reduce CAD must address as many of these factors as possible in an effort to not only reduce the extent and severity of CAD but also limit the extent of myocardial damage (MI, congestive heart failure, death), which is after all the reason for treating CAD. Failure to reduce damaged myocardium, while altering the appearance of blood flow in the larger arteries, ignores the true consequences of CAD.

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