

Angina and Coronary Ischemia Are the Result of Coronary Regional Blood Flow Differences

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Background—The current definition of angina is cardiac pain caused by decreased blood flow, presumably through a narrowed coronary artery, resulting in inadequate coronary blood flow for the needs of the heart at the time of chest pain. If angina is truly due to an “anatomic” narrowing only, then 100% of angina patients would be expected to have some degree of coronary stenosis versus the observed 15-30% currently reported. It is known that coronary artery disease resulting from narrowing of coronary arteries, intimal plaque deposition (vulnerable plaque), and/or endothelial dysfunction decreases coronary flow reserve (CFR). A diseased coronary artery with decreased CFR has by definition “physiologic” narrowing regardless of anatomic findings. If angina is not limited to anatomically reduced blood flow but is instead due to physiological differences in coronary regional blood flow, then these differences, should be associated with anginal symptoms with or without anatomically detectable coronary stenosis.

Methods—To test this hypothesis, coronary angiography and MPI were performed on 72 individuals (39 men, 33 women) with anginal symptoms.

Results—Patients served as their own controls for expected changes in blood flow. Results were compared with angiographic data, which revealed detectable narrowings in 18 of 72 (25%) patients. When the cumulative ischemic burden (CIB) was analyzed, there was a statistical increase (ranging from $p < 0.05$ to < 0.001) in regional ischemic burden (RIB) as the number of diseased vascular beds increased, regardless of the presence or absence of angiographically detectable narrowings.

Conclusions—These angiographically identified narrowings (coronary lumen disease/CLD) did not account for the incidence of anginal symptoms reported in this or recent studies. Individuals with reduced CFR have clearly been shown to have reduced vasodilatory response with subsequent differences in coronary regional blood flow, despite showing an absolute increase in coronary blood flow following high-dose dipyridamole (HDD). Such differences demonstrate “physiologic” narrowings, due to “anatomic” narrowings (CLD), intimal (vulnerable) plaque identified by intravascular ultrasound (IVUS), endothelial dysfunction, small- and medium- sized artery disease or other causes not yet elucidated, which match anginal symptoms. As CIB and RIB differences increased, so did the number of anginal symptoms, and MPI documented diseased coronary arterial beds. These results support the hypothesis that angina is due to differences between regional coronary blood flow, which represents a “physiologic” narrowing that may or may not have an anatomically detectable component.

Key Words: Angina • Nuclear Cardiology • Coronary Reserve

Background

Coronary artery disease (CAD) remains the number 1 cause of death worldwide with nearly 1 million Americans (1 every 10 seconds) dying from heart disease yearly, and since 1995, more

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women have died from heart disease than men. Diagnostic evaluation of CAD has focused on several approaches, including coronary angiography (catheterization), which utilizes contrast media injections to detect coronary narrowings (percent diameter stenosis/%DS), previously thought to be present in all individuals with CAD. By tradition, angina has been defined as the symptoms produced as a consequence of decreased blood flow proceeding through a stenosed coronary artery. However, recently it has been demonstrated¹⁻³ that most myocardial events (70%) occur in arteries with little or no detectable %DS and that only a small fraction (15-30%) of patients with angina have truly detectable abnormalities⁴⁻⁷ by angiography. Other diagnostic studies,⁸⁻¹⁰ including intravascular ultrasound (IVUS), endothelial function studies, and myocardial perfusion imaging (MPI), have revealed CAD in these individuals, supporting the hypothesis¹¹ that angina is not strictly due to anatomic narrowings within the lumen of coronary arteries.

The question remains, however, if significant %DS exists in only 15-30% of those individuals with angina, but angina is presumed to be due to decreased flow through a narrowed coronary artery, then why do the remaining individuals have angina? Furthermore, it is well known that individuals undergoing diagnostic testing with myocardial perfusion imaging (MPI) using either single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging can have anginal symptoms^{12,13} following the "stress" part of the study. When "stress" was performed with use of exercise treadmill, and both heart rate and blood pressure increased, the idea of decreased blood flow through a narrowed coronary artery with increased oxygen demand continued to appear to be valid. However, with the use of pharmacologic agents like dipyridamole and adenosine, which affect coronary blood flow through vasodilation without changing the oxygen demand of the heart, there should be no angina, since vasodilation would carry more, and not less, blood through the coronary arteries. In work published in 1995, the use of high-dose dipyridamole (HDD) was associated not only with increased blood flow through coronary arteries but also with an increase in reported anginal symptoms¹⁴⁻¹⁷ in people with true coronary artery lumen disease as documented by both visual and quantitative coronary angiography (QCA).

This suggests that the cause of angina is due not solely to an "anatomic" narrowing as previously suspected, but rather to a "physiologic" narrowing that results from more than just anatomic lumen narrowing alone. In the presence of diseased coronary arteries caused by "anatomic" narrowing, endothelial dysfunction, vulnerable plaque, and/or other causes,^{10,18} there is a reduction in the arteries' ability to increase (vasodilate) coronary flow (coronary flow reserve/CFR) upon demand,^{19,22} regardless of whether that demand to increase blood flow is due to exercise or pharmacologic stimuli. It is this difference in CFR that is truly being tested via MPI, since CFR is the comparison of maximal coronary blood flow to resting flow. The ability to detect CAD by MPI is made possible by detection of differences in coronary blood flow as demonstrated by differences in tracer activity between resting and "stressed" conditions. Most nuclear laboratories do not determine absolute radioactive tracer counts, which represent coronary blood flow, but rather depend on differences in images in either gray-scale or color images to make their diagnostic decisions. Nonetheless, the quantitation of flow²³⁻²⁹ is part and parcel of every study whether applied directly or not.

Given the idea that diseased coronary arteries dilate less than nondiseased arteries, then one would expect differences in coronary blood flow from dipyridamole to be due to differences

in relaxation (vasodilation) and subsequent blood flow, which can be detected by differences in tracer activity. This can be thought of as a relative functional narrowing or decreased ability to increase CFR, which cannot be detected by anatomic methods. In an effort to test the hypothesis that angina is due to differences in coronary regional blood flow regardless of the presence or absence of coronary lumen disease (CLD), we studied 72 people with angina, using both coronary angiography to look for coronary lumen disease (anatomic narrowing) and MPI to look for differences in coronary regional blood flow. These differences were then compared with patient symptoms to determine the relationship between anginal symptoms.

Methods

Seventy-two people were studied (39 men and 33 women ranging in age from 29 to 71 years). All were suspected of having CAD based on anginal symptoms, which consisted of retrosternal pressure/pain, dyspnea at rest or with exertion, and discomfort in the chest radiating to the neck and/or left upper limb. Patients were enrolled for diagnostic evaluation after completion of Institutional consent forms. Pulmonary function studies were performed to exclude individuals with asthma who would be unable to be pharmacologically "stressed" with dipyridamole. Subjects were not studied if they were pregnant, had aortic stenosis, unstable angina, or a cardiomyopathy. All patients were studied in the fasting state and did not take medications the day prior to, or the day of, the MPI study.

Angiographic Studies

Angiographic evaluation was performed on each of the individuals by using the Judkins approach following standard procedures previously described,^{5,6,12,21} including determination of percent diameter stenosis and of endothelial function and intravascular ultrasound (IVUS) evaluation.¹¹

Resting Myocardial Perfusion Imaging with Sestamibi

Myocardial Perfusion Imaging was performed using a standardized protocol¹⁴ as outlined in Figure 1. A 22-gauge Jelco intravenous catheter was placed antecubitally and remained for the duration of the testing. Resting studies were performed first (A.M. study) to determine if evidence of prior myocardial damage existed as demonstrated by decreased tracer activity. The studies consisted of the intravenous (IV) administration of 10-15 mCi of Sestamibi (dosed by patient weight) followed by a 15 cc normal saline flush to ensure complete infusion of the isotope. Image acquisition was initiated 30 minutes later, allowing for adequate clearance from the blood pool and myocardial activity. A Siemens orbiter model 6601 (75 PHT) was used for SPECT image acquisition. A low-energy high-resolution (LEHR) 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 (RAO) and ending in the left posterior oblique (LPO) position, for a total of 34 minutes' acquisition time. Images were reconstructed by using standard back projection with reconstruction of short-axis, horizontal and vertical long-axis, and bull's-eye views.

High-Dose Dipyridamole (HDD) & Myocardial Perfusion Imaging (MPI)

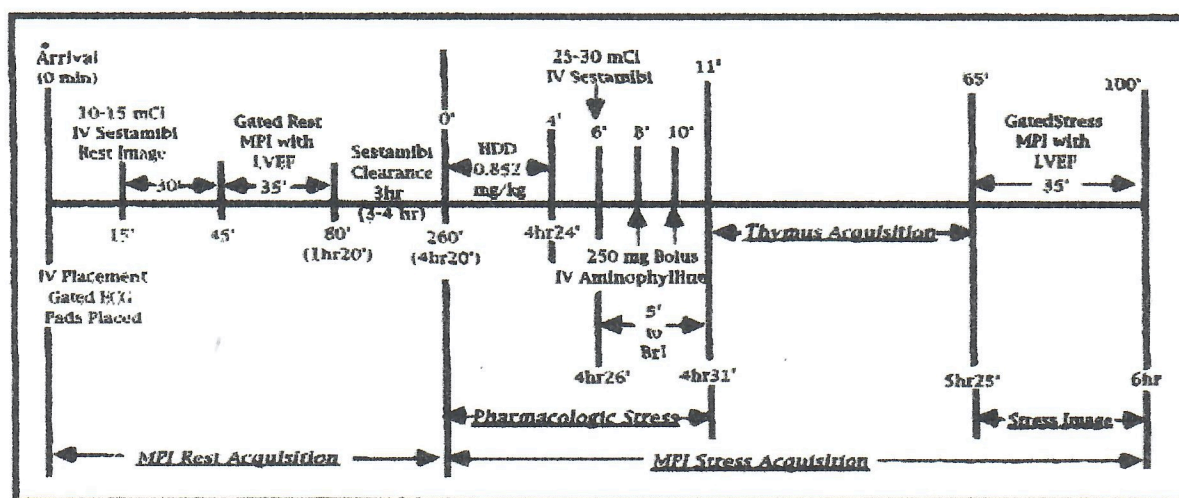


Figure 1. Myocardial perfusion imaging (MPI) protocol. The protocol for administration of resting and "stress" image acquisitions by use of SPECT imaging with high-dose dipyridamole (HDD) and Sestamibi. Dosages of Sestamibi and HDD are based on patients' body weight. The vasodilatory effect of HDD with aminophylline is not reversed until adequate clearance time (2 minutes) has been provided for Sestamibi myocardial imaging uptake.

High-dose Dipyridamole Myocardial Perfusion Imaging with Sestamibi

Approximately 4 hours after the initial infusion of Sestamibi, the intravenous catheter was prepped and connected to a Graseby 3400 infusion pump for delivery of the prescribed dose of dipyridamole. Continuous electrocardiographic (ECG) monitoring was maintained throughout the period of pharmacologic "stress" and 4 minutes after HDD infusion, ensuring resolution of any symptoms. Heart rate and blood pressure measurements were recorded every 2 minutes from beginning to end of ECG monitoring. A total dose of 0.852 mg per kg body weight of dipyridamole was infused over 4 minutes followed by a 5-15 cc flush of normal saline to ensure complete delivery. Two minutes later (Figure 1) 25-30 mCi of Sestamibi (determined by patient weight per package insert) was administered followed by 15 cc normal saline flush. Patient symptoms were reported and reversed with aminophylline bolus(es) followed by saline flush as previously described. Cardiac image acquisition was initiated 30-60 minutes later¹⁴ and performed in the same manner described above for resting image acquisition and reconstruction. Reversal of the vasodilatory effect of HDD was accomplished with 250 mg boluses of aminophylline as shown in Figure 1 and described previously. Of importance for accurate determination of regional blood flow and MPI is the amount of time required between infusion of Sestamibi and the necessary circulation clearance time (2 minutes) before aminophylline should be given.

Quantification of Coronary Regional Blood Flow

Determination of expected increases in coronary blood flow (Q value) following HDD (Q_s) was compared with baseline (Q_r) flow. Quantification of coronary flow (Q) was determined for each patient by use of both HDD and resting image analysis. Maximum activity/flow was determined by histogram analysis of greatest radioactive counts. The area of greatest absolute count activity was then interrogated by use of a template (10×10 pixel ≈ 10 mm $\times$ 10 mm) region of interest (TROI) to ensure that all measurements were made with the same size region. The greatest activity/flow (GA) at stress and rest were measured (described below) and divided by the amount of isotope given (millicurie/mCi), since the flow/activity detected is due both to differences in blood flow and differences in the amount of isotope given. Since the resting and "stress" doses of isotope were different, dividing the activity by the amount of mCi at rest and stress eliminates differences caused by varying amounts of isotope given, leaving differences due to changes in coronary blood flow. Maximal blood flow at stress (HDD) and rest were measured and standardized as shown in equations 1 and 2 below.

$$Q_s = GA \text{ at stress/pixel/mCi} = GA\text{-CPM stress} \quad (1)$$

$$Q_r = GA \text{ at rest/pixel/mCi} = GA\text{-CPM rest} \quad (2)$$

Where Q_s is flow at stress (HDD), Q_r is flow at rest, GA is greatest activity, $GA\text{-CPM stress}$ is greatest activity in counts/pixel/mCi following HDD and $GA\text{-CPM rest}$ is greatest activity in counts/pixel/mCi at rest. This allowed for a comparison of blood flow for each individual based on changes in blood flow only. To determine the expected increase in blood flow for each individual, a "flow (Q value) value" was determined by dividing the resting flow into the stress flow as shown in equation 3.

$$Q \text{ value} = \frac{Q_s = GA\text{-CPM stress}}{Q_r = GA\text{-CPM rest}} \quad (3)$$

Where Q value is the expected increase in coronary flow/activity as a result of vasodilation.

Determination of Regional Blood Flow (Q Regional) Differences

Each rest and stress image was analyzed by using the template shown in Figure 2 to ensure that identical TROIs were compared in both the resting and stressed states. This approach eliminated adjustment (intentional or unintentional) of images, which could have biased calculations. Analysis of regional blood flow from a TROI was measured as discussed above. Fourteen TROIs were assessed at rest and stress with total counts determined as shown in Figure 3. The mean (average) activity (counts) was measured and calculated per pixel. This was further standardized by dividing this by the mCi given for both the resting and HDD study as described above. Using this approach the regional flow/activity (Q regional) was determined for each of the 14 regions at rest (rest-CPM) and stress (HDD-CPM) conditions by use of the following formulas:

$$Q \text{ regional HDD (stress)} = \mu \text{ counts/pixel/mCi} = HDD\text{-CPM} \quad (4)$$

$$Q \text{ regional rest} = \mu \text{ counts/pixel/mCi} = rest\text{-CPM} \quad (5)$$

Where μ equals the mean value.

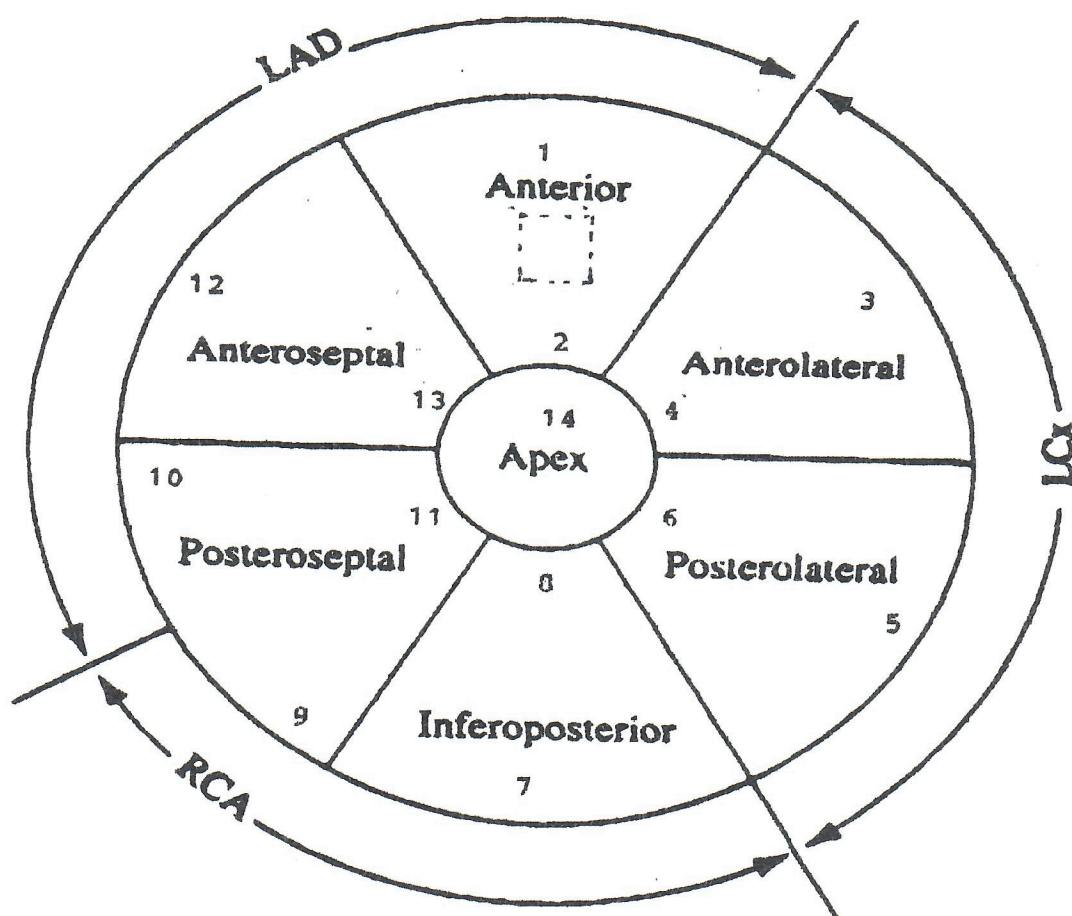


Figure 2. Template regions of interest (TROIs). In order to eliminate operator manipulation of data and a potential source of errors, 14 TROIs were analyzed for each resting and HDD image by using the following template. Region 14 sits at the middle of the apex region. Each TROI is 10 by 10 pixels in size and represents a 10-by 10-mm region of interest.

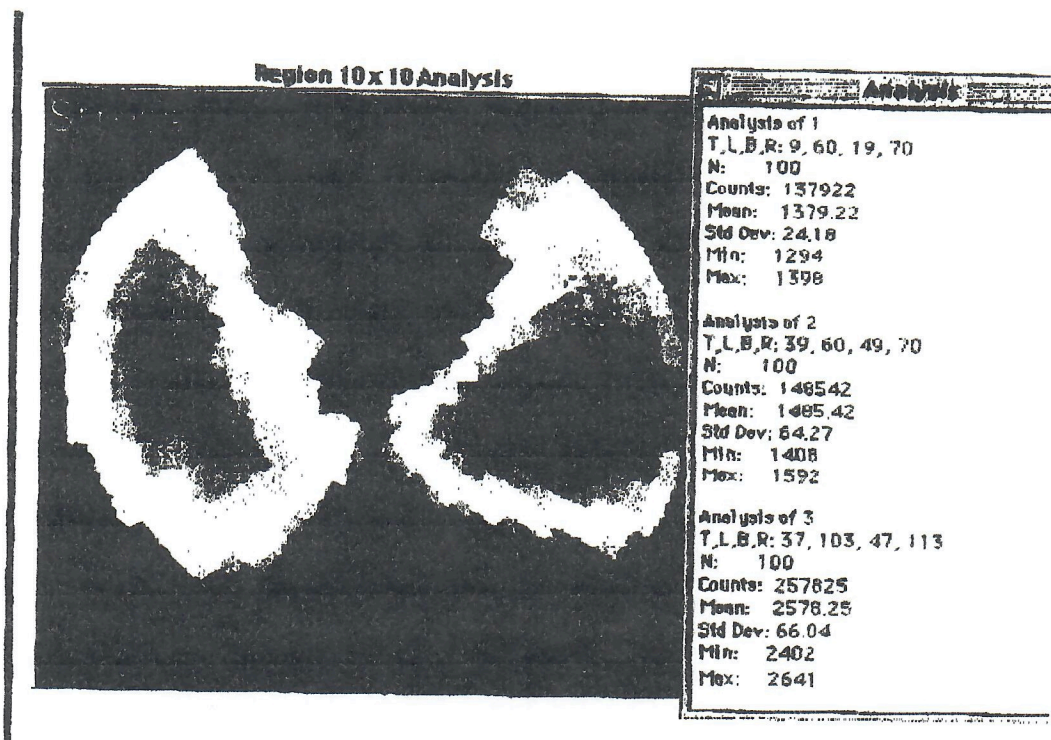


Figure 3. Example of quantitation of radioactive counts. This example shows a representation of template region of interest (TROI) 1, 2, and 3 analysis (as displayed in Figure 2) in a patient following HDD (stress). Each TROI represents a 10-by-10 pixel region ($n=100$ pixels) with the mean $\pm$ standard deviation reported for each TROI along with the actual counts, minimal and maximal values for regional blood flow in each of the 3 TROIs. The mean $\pm$ standard deviation for the TROI was 1379.22 ± 24.18 for region 1, 1485.42 ± 64.27 for region 2, and 2578.25 ± 66.04 for region 3 counts. Decreased regional blood flow is present in regions 1 and 2. These values were then divided by the mCi Sestamibi given to determine the HDD-CPM (equation. 4) for this particular region, which were then divided by the results for each of these regions measured at rest to determine the regional blood flow as compared to the expected flow for this patient.

To determine the change in regional blood flow for each of the 14 TROIs, the regional resting flow was divided into the regional stress flow obtained following HDD infusions, as follows:

$$Q_{\text{regional value}} = \frac{Q_{\text{regional HDD (stress)}} \approx \text{HDD-CPM}}{Q_{\text{regional rest}} = \text{rest-CPM}} \quad (6)$$

Where $Q_{\text{regional value}}$ shows the actual increase in blood flow seen with vasodilation of regional coronary arteries.

Comparing Regional Blood Flow Differences to Expected Increases in Coronary Blood Flow
Based on each patient's expected increase in coronary blood flow (*Q* value), assuming no regional coronary blood flow limitations, then regional (*Q* regional) blood flow should equal the expected (observed) increase in blood flow with each individual as his/her own reference. To determine regional blood flow differences, the following equation was applied:

$$Q \text{ ratio} = \frac{Q \text{ regional (observed)}}{Q \text{ value (expected)}} \quad (7)$$

Where *Q* ratio reflects the result of what is observed regionally following HDD with that expected for each individual.

Cumulative Ischemic Burden

In each of the arterial regions (Figure 2), ischemic burden of a region (IB) can be determined by subtracting the *Q* regional (observed) value from the *Q* (expected) value:

$$IB = Q \text{ value minus } Q \text{ regional} \quad (8)$$

The CIB is determined by adding the IB of each of the major vascular beds together.

Statistical Analysis

Radioactive counts were quantified directly from computer analysis with calculation of mean counts as discussed above. Patient response to pharmacologic stress (HDD) was recorded along with detectable regional MPI and requirement for reversal of HDD for symptom relief. Symptom reports were then compared with regional blood flow differences to determine the relationship. Cumulative ischemic burdens were determined and nonpaired Student's *t* test was performed to determine differences in CIB and the number of diseased coronary arteries. Graphic comparison was made between "*Q* regional" results for both regions of ischemia and infarction.

Results

Seventy-two individuals (39 men and 33 women between 29 and 71 years of age) underwent diagnostic evaluations for CAD after presenting with anginal symptoms. Of these, 18 of 72 (25%) had detectable coronary lumen stenosis (CLS). Five patients (7%) had detectable endothelial dysfunction. Sixty-eight (94%) had plaque detectable by IVUS. No statistical differences were detectable based on age, sex, race, or types of symptoms reported. With use of angiography, endothelial function, and IVUS, 70 of the 72 patients were diagnosed as having CAD.

Non-q-wave myocardial infarction (MI) was identified in 63 of the 72 (87%) individuals with 3 others having q-wave MIs. One of the 3 patients with q-wave MIs had angiographically detectable narrowings. Measurements of absolute (quantitative) counts initially determined by histogram analysis were confirmed by analysis of TROIs as shown in Figure 3. The detected increase in coronary blood flow (*Q* value) was calculated following measurement of isotope activity for each individual as described in equation 3 with the absolute values shown in Table I. This "*Q* value" represents the expected increase in blood flow, which should occur throughout

healthy regions of the heart. Despite expected increased blood flow following HDD, patients with triple vessel CAD actually demonstrated a reduction in "Q value." This means that in these individuals the actual blood flow, as quantitatively measured, fell following attempts to increase blood flow through vasodilation. This follows the expected results seen when CFR falls below 1.¹⁹⁻²²

Seventy of the 72 (97%) individuals had evidence of myocardial ischemia as measured with reductions in regional (Q regional) blood flow. Sixty-six of the 70 (94%) reported anginal symptoms that matched reductions in "Q regional." The remaining 4 had reductions in regional blood flow in only 1 coronary artery and a CIB of 0 to 0.1 as shown in Table I. Table I and Fig. 4 show the results of cumulative ischemic burdens, which were determined by summing the IBs (equation 8) together for each individual. As the number of diseased arterial beds increased (Table I, Figure 4), so did the CIB and the need for reversal of the vasodilatory effect. As shown in Table II, differences in CIB were statistically significant for all comparisons except differences between 1- and 2- vessel disease.

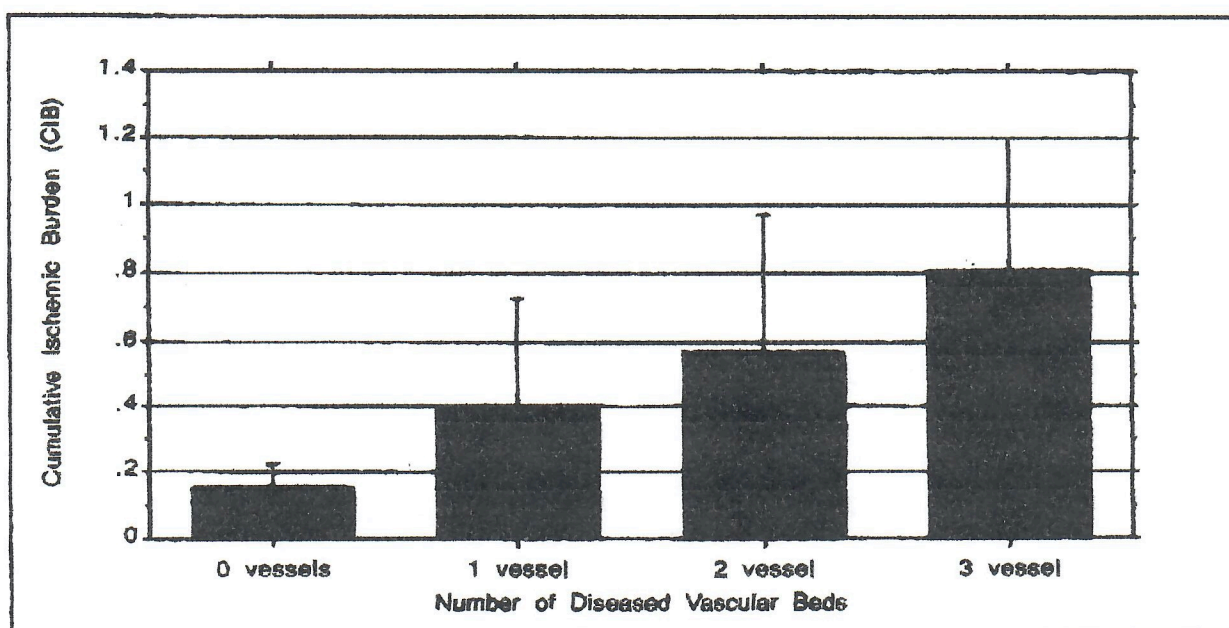


Figure 4. Cumulative ischemic burden (CIB). The CIB as described in the text was determined for each individual and compared on the basis of the number of diseased coronary arteries present. As shown in Table II, statistical differences were noted between all groups except for 1- and 2-vessel disease, which approached but did not reach statistical significance.

Table 1. Quantitative results from 72 individuals.

Q value	Q ratio (MI)	Q ratio (ischemia)	CIB 0 vessels	CIB 1 vessels	CIB 2 vessels	CIB 3 vessels
1.4	1.3	0.7				0.9
1.3	1.3	0.8		0.3		
2.1	1.1	0.8				0.7
1.3	1.2	0.9	0.1			
1.1	2.4	0.6				0.9
1.2	1.2	0.9			0.2	
1.5	1.2	0.8				0.8
1.3	1.2	0.8			0.4	
1.1	1.3	0.8			0.5	
1.5	1.2	0.9			0.2	
1.6	1.4	0.8				0.5
1.2	1.3	0.7			0.8	
1.2	1.2	0.6				0.7
1.4	1.3	0.9		0.0*		
1.5	1.3	0.7			0.4	
1.2	1.4	0.9			0.1	
2.0	1.1	0.8			0.7	
1.3	1.5	0.9			0.2	
1.2	1.1	0.4				1.9
1.4	1.3	0.7				0.6
1.4	1.4	0.9			0.5	
1.5	1.1	0.9			0.2	
1.9	1.2	0.8				0.7
1.6	1.1	0.5			2.1	
1.3	1.5	0.7				0.8
1.5	1.1	0.8			0.8	
1.8	1.1	0.6				1.3
0.9	1.2	0.9			0.2	
1.6	1.1	0.8				1.1
1.3	1.3	0.9		0.1		
1.0	1.1	0.7		0.6		
1.4	1.1	0.7				0.7
1.5	1.3	0.7			0.9	
1.3	1.2	0.6			1.1**	
1.2	1.2	0.6		0.1*		
1.4	1.4	0.8			0.5	
1.3	1.3	0.9			0.3	
1.6	1.2	0.7				1.4
1.3	1.2	0.7			0.6	
0.8	1.4	0.9		0.3***		
1.6	1.1	0.8		0.8		
1.2	1.3	0.9		0.1		
1.4	1.1	0.7				0.6
1.1	1.2	0.8			0.5	
2.5	1.1	0.8			1.3	
1.6	1.2	0.8				0.6
1.6	1.4	0.9		0.1*		
1.9	1.2	0.7			1.0	
1.1	1.1	0.4				1.3
1.4	1.2	0.8			0.4	
1.3	1.4	0.9		0.1*		
1.5	1.3	0.8			0.4	
1.7	1.1	0.9				0.6
1.2	1.3	1.0	0.2			
1.2	1.4	0.9			0.7	
1.3	1.2	0.9				0.3
1.1	1.1	0.9			0.3	
1.6	1.1	0.9			0.5	
1.2	1.2	0.8				0.6
1.1	1.2	0.8				0.5
1.4	1.1	0.7		0.9		
1.7	1.1	0.8			0.8	
1.4	1.1	0.9			0.3	
1.4	1.1	0.8		0.8		
1.5	1.1	0.7				0.7
1.3	1.2	0.7		0.6		
1.4	1.1	0.8				0.8
1.1	1.4	0.9			0.2	
1.1	1.2	0.9				0.2
1.5	1.1	0.8			0.6	
1.6	1.4	0.8			0.7	
1.3	1.1	0.6		0.8		

* patients who had no anginal symptoms, ** case study 1, *** case study 2.

Table II. Differences in cumulative ischemic burdens

Comparison	Statistical Significance
0- and 1-vessel disease	p = 0.05
0- and 2-vessel disease	p = 0.001
0- and 3-vessel disease	p = 0.001
1- and 2-vessel disease	p = NS
1- and 3-vessel disease	p = 0.005
2- and 3-vessel disease	p = 0.05

NS is not statistically significant.

Specific case examples added additional insight and proof of the effect of "Q regional" differences through the inadequate preparation of 2 of the individuals for their initial studies. In the first example, the patient was advised to have nothing to eat before the study but drank caffeinated coffee immediately before his arrival for the HDD part of the study. His "Q value" was initially 1.2, and following administration of HDD, he reported no anginal symptoms. No regional ischemia (Q regional) was detectable and no antidote (aminophylline) was required. The following day he was restudied, this time assuring he did not drink coffee before the study. As shown in Table I (case study 1), his "Q value" was 1.3 the following day (improved vasodilatory effect compared with the day before) and both his "Q regional" dropped and his CIB increased to 1.1 with 2-vessel disease clearly documented on his MPI study. More importantly, on this day he reported chest discomfort left anterior descending (LAD) and nausea right coronary artery (RCA), which required reversal with a 250 mg bolus of intravenous aminophylline.

A second case study demonstrated the opposite scenario, with the second individual eating before coming to the laboratory. The amount of blood available for myocardial perfusion was decreased secondary to diversion of blood to the gastrointestinal system. On the initial resting study, blood flow was uniformly decreased on coronary evaluation. Following HDD infusion, a greater than expected increase in coronary blood flow was seen, since the resting flow (equations 2 and 3) had been artificially reduced and the "Q value" was 1.5. The initial "Q regional" differences were greater as a result, and the CIB was 1.0, compared with a CIB of 0.3 the following day when no food was eaten before the study. "Chest discomfort" was reported during the first study but not the later.

Another method used for blood flow differences was the "Q ratio" (equation 7), which compares the regional blood flow to expected blood flow. As shown in Table I and Figure 5, differences between ischemic regions and expected blood flow showed a ratio of less than 1 regardless of the actual "Q value" which varied from patient to patient. Ratios of less than 1 demonstrated decreased regional blood flow and anginal symptoms. As the regional ischemia

worsened, the symptoms became worse and required reversal with intravenous aminophylline. Similarly, regions of myocardial infarction are associated with decreased uptake of Sestamibi at rest secondary to a decrease in mitochondrial activity. This results in an independent reduction in rest CPM and a greater "Q regional" value (equation 6) and an increase in "Q ratio" (equation 7). This approach allows for the independent assessment of regional ischemia and infarction. As shown in Table I and Figure 5, regions of infarction have "Q ratios" of greater than 1. Also noted, was a reduction in "Q values" for regions of Q-wave MIs, although the difference was not statistically significant.

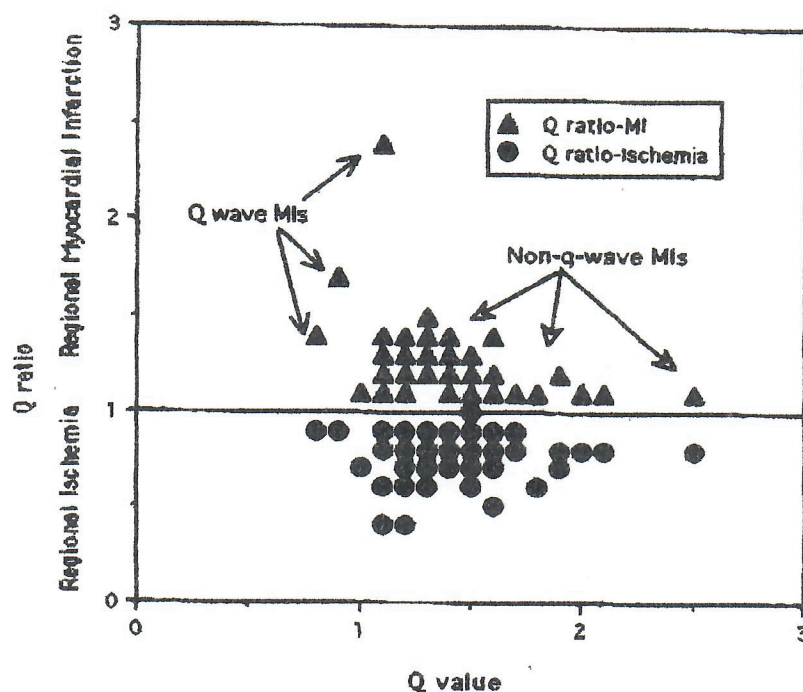


Figure 5. A comparison of Q ratio to Q value. The independent assessment of regions of ischemia and myocardial infarction can be determined upon the basis of the Q ratio, which was compared with the Q value (independent variable for each patient) as shown above. The "Q ratio" was less than 1 when myocardial ischemia and anginal symptoms were reported regardless of the independent "Q value" for any given patient. Likewise, myocardial infarctions were noted when the "Q ratio" was greater than 1, with Q-wave MIs tending to have both elevated "Q ratios" and lower "Q values."

Discussion

The determination of CLD using angiographic techniques was limited to 25% of the individuals studied. Assessment of endothelial dysfunction (7%) and intimal thickening (94%) increased the detection of CAD to 97% of those studied. Similarly, the quantification of coronary regional blood flow using MPI demonstrated CAD in 97% of those studied. In fact, the 2 patients whose myocardial perfusion images and regional coronary blood flow were determined to be "normal" were also found to have no abnormalities through use of angiography, IVUS, and endothelial function; raising a question regarding other, unidentified causes of angina.

The detectability of CAD by MPI has previously focused on looking for differences in gray-scale or color-scale images. However, the actual computer application of these images is and has been dependent on the quantification of radioactive counts in a region of myocardium. These counts are dependent on differences in coronary blood flow^{23,29} and the amount of isotope given. Independent assessment of infarction and blood flow is possible because infarcted tissue need not be associated with totally occluded arteries except at the time of actual infarction, and no patients were evaluated while having an acute cardiac event. With the exclusion of totally occluded arteries, the differences seen can be accounted for on the basis of differences in coronary regional blood flow and differences in the amount of isotope given.

To standardize the results seen, each individual received a resting and "stress" dose of isotope based on the manufacturer's (DuPont) recommendation determined by body weight. This approach eliminates differences due to patient size (body habitus). Second, the differences in isotope were standardized by initially quantitating the amount of radioactivity present in a TROI, which could not be changed by operators. This guaranteed that the same identical regions were being compared between patients. The actual quantitation was measured as shown in Figures 2 and 3. With this approach, the actual radioactive counts were then divided by the amount of isotope (mCi) given for resting and HDD studies, which gave the counts per pixel per millicurie as defined in equations 1 and 2, thereby effectively removing differences due to the amount of isotope used. The effective difference between maximal flow obtainable with HDD and flow at rest was determined (equation 3) for each individual, making each individual his/her own standard of comparison, thereby eliminating other unpredictable variables.

This approach of using patients as their own predictors of changes in blood flow following the administration of HDD allowed the differences in regional blood flow to be compared to the expected blood flow for each individual. While "anatomic" stenosis may not have been detected, differences in regional blood flow were. These associated changes in regional blood flow increased as the severity of disease increased. This increase in regional blood flow differences could be compared individually and cumulatively (CIB) and matched the development of anginal symptoms in 94% of the subjects. The remaining 4 individuals did not appear to have sufficiently impaired regional blood flow to produce symptoms.

These differences in regional blood flow can be thought of in many terms, including independently reduced "Q regional," increased CIB, and/or "Q ratios" of less than 1. Regardless of the term used, differences in coronary regional blood flow were associated with symptoms, which reversed with aminophylline administration, which restored resting/baseline blood flow, effectively eliminating regional increases/differences in coronary blood flow. Symptoms also could not be related to increased cardiac workload, since resting and "stress" studies were performed in the supine position with differences in blood flow being produced by the vasodilatory effect of the HDD. Any cause of CAD sufficient to produce symptoms would be expected to inhibit the vasodilatory effect of coronary arteries and their ability to increase coronary blood flow on demand.

Conclusion

Anginal symptoms vary from person to person depending on individual differences in the perception of pain/discomfort/problems and the region and quantity of myocardium affected. By convention the definition³⁰ of angina has been chest pain "caused by coronary disease." Despite

our expectations that this coronary disease be evidenced as an "anatomic" narrowing, the definition of angina does not state this. More importantly, the detectability of significant localized coronary arterial narrowings is frequently not noted despite the presence of anginal symptoms. While the actual percent of cases with detectable %DS may be a point of contention, it is now clear that it is not always present and is less common than previously thought. Coronary flow reserve has long predicted changes in a coronary artery to increase its blood flow upon demand with reduced CFR predicting symptoms.¹⁹⁻²² However, this definition in and of itself does not stipulate that anatomic narrowings need to be present, and the acceptance of Prinzmetal's angina is a classic example of the prior acceptance that narrowing need not be present.

This study clearly demonstrates that differences in coronary regional blood flow are responsible both for ischemic changes and angina, with and without detectable coronary lumen disease. These differences in regional blood flow were shown to be present when anginal symptoms were reported, with an increase in symptoms reported with increased CIB requiring reversal of regional blood flow differences by use of aminophylline. The regional blood flow differences observed could not be accounted for on the basis of age, race, sex, body weight, myocardial oxygen demand, or percent diameter stenosis. These regional differences in blood flow represent a "physiologic" narrowing and appear to be the basis for anginal symptoms.

With this as the basis for understanding the cause of angina, then individuals receiving benefit from medications are probably receiving enhanced vasodilation in those areas where regional blood flow was reduced. Chronic angina, which is typically associated with fewer symptoms, has the greatest likelihood of developing collateral circulation (angiogenesis), which would result in communication of regions receiving good blood supply with those receiving poorer blood supply. This communication would result in decreased regional blood flow differences without an actual improvement in overall blood supply and would explain why patients with chronic heart disease tend to have less pronounced angina once collateral circulation has occurred, although this is clearly only 1 possible contributing explanation. The use of gene therapy has been shown to reduce anginal symptoms in patients studied by use of MPI. While the overall coronary blood flow is not increased in these individuals, the development of collateral circulation (angiogenesis) promotes a sharing of coronary blood supply with a reduction in coronary regional blood flow differences. Subsequently, interventions that reduce coronary regional blood flow differences may be expected to reduce anginal symptoms while those that augment differences would increase angina. Finally, and perhaps most importantly, in those individuals who have anginal symptoms but undetectable narrowings angiographically, further evaluation (IVUS, endothelial studies, MPI) is indicated to determine the cause of regional blood flow differences producing the patients' angina.

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