Physiological Basis for Angina and ST-Segment Change

PET-Verified Thresholds of Quantitative Stress Myocardial Perfusion and Coronary Flow Reserve

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OBJECTIVES This study aimed to determine the quantitative low-flow threshold for stress-induced perfusion defects with severe angina and/or significant ST-segment depression during dipyridamole hyperemia.

BACKGROUND Vasodilator stress reveals differences in regional perfusion without ischemia in most patients. However, in patients with a perfusion defect, angina, and/or significant ST-segment depression during dipyridamole stress, quantitative absolute myocardial perfusion and coronary flow reserve (CFR) at the exact moment of definite ischemia have not been established. Defining these low-flow thresholds of angina or ST-segment changes may offer insight into physiological disease severity in patients with atherosclerosis.

METHODS Patients underwent rest–dipyridamole stress positron emission tomography (PET) with absolute flow quantification in ml/min/g. Definite ischemia was defined as a new or worse perfusion defect during dipyridamole stress with significant ST-segment depression and/or severe angina requiring pharmacological treatment. Indeterminate clinical features required only 1 of these 3 abnormalities. The comparison group included patients without prior myocardial infarction, or angina or electrocardiographic changes after dipyridamole.

RESULTS In 1,674 sequential PET studies, we identified 194 (12%) with definite ischemia, 840 (50%) studies with no ischemia, and 301 (18%) that were clinically indeterminate. A vasodilator stress perfusion cutoff of 0.91 ml/min/g optimally separated definite from no ischemia with an area under the receiver-operator characteristic curve (AUC) of 0.98 and a CFR cutoff of 1.74 with an AUC = 0.91, reflecting excellent discrimination at the exact moment of definite ischemia.

CONCLUSIONS Thresholds of low myocardial vasodilator stress perfusion in ml/min/g and CFR sharply separate patients with angina or ST-segment change from those without these manifestations of ischemia during dipyridamole stress with excellent discrimination. Stress flow below 0.91 ml/min/g in dipyridamole-induced PET perfusion defects causes significant ST-segment depression and/or severe angina. However, when the worst vasodilator stress flow exceeds 1.12 ml/min/g, these manifestations of ischemia occur rarely.   (J Am Coll Cardiol Img 2011;4:990–8) © 2011 by the American College of Cardiology Foundation

During coronary vasodilator stress, most patients experience hyperemia in excess of myocardial metabolic need, because vasodilating agents uncouple coronary blood flow from demand. However, in a subset of patients, myocardial perfusion drops below metabolic demand in a portion of the myocardium, particularly in the subendocardium (1). Such patients may experience severe angina, significant ST-segment depression, and an imaging abnormality during

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vasodilator stress. Therefore, physiological imaging during vasodilator stress associated with these symptoms reflects absolute myocardial perfusion and coronary flow reserve (CFR) at the exact moment of definite ischemia. Defining these low-flow thresholds of ischemia may offer insight into physiological disease severity in patients with advanced atherosclerosis, as contrasted with young normal volunteers (2) or intermediate values in the larger population with subclinical, nonobstructive coronary atherosclerosis.

METHODS

All patients underwent rest–dipyridamole stress myocardial perfusion positron emission tomography (PET) with absolute flow quantification at the Weatherhead PET Center for Preventing and Reversing Atherosclerosis of the University of Texas Medical School at Houston and Memorial Hermann Hospital. Subjects gave written informed consent approved by the institutional review board. Standard demographic information, cardiac history, and risk factors were recorded. Patients represented the entire spectrum of coronary disease, including assessment or follow-up of known coronary artery disease (CAD), second opinions on revascularization procedures, prior positive stress tests, coronary calcification by computed tomography (CT), chest pain or other symptoms, or risk factors.

PET acquisition protocol. Our acquisition and processing protocol has been extensively described (2–5). Patients were instructed to fast for 4 h and abstain from caffeine, theophylline, and cigarettes for 24 h. Cardiac imaging with prospective measurement of absolute flow was performed between March 2007 and July 2010 using a Discovery ST PET scanner with hybrid 16-slice CT scanner (GE Healthcare, Waukesha, Wisconsin) in 2-dimensional

mode with an in-plane resolution of approximately 6 to 7 mm full width at one-half maximum (6).

Rest emission data were obtained over 7 min beginning immediately upon intravenous injection of 35 to 50 mCi (1,295 to 1,850 MBq) of generator-produced Rb-82 (Bracco Diagnostics, Princeton, New Jersey). Images contained 24 to 60 million total counts, of which 12 to 30 million were true coincidence counts. The first 2 min of the emission images were binned to form the arterial input data. The last 5 min of the emission images were binned to form the myocardial uptake data. Immediately after completion of the resting scan, dipyridamole (142 μg/kg/min) was infused for 4 min. Four minutes after completion of dipyridamole infusion, the same dose of radiotracer was given. Stress emission images were acquired for 7 min and binned into arterial and myocardial images as for the resting scan. CT scans for attenuation correction were acquired before rest and after stress emission imaging and aligned to emission data as previously reported (3).

Severe angina relieved only after intravenous aminophylline, sublingual nitroglycerin, and/or intravenous metoprolol was recorded, distinct from nonischemic chest symptoms due to dipyridamole. Continuous 12-lead electrocardiogram (ECG) monitoring during dipyridamole stress identified significant, >1-mm ST-segment depression. Hemodynamic parameters of heart rate and blood pressure were recorded at rest and during dipyridamole stress.

To demonstrate the universality of our findings, distinct from hardware configurations or radionuclides, we also performed a minority of studies using 2 rotating-rod PET scanners. Between February 1993 and May 1997, 538 studies were performed on the original University of Texas cesium fluoride scanner (7). Between September 2006 and April 2010, 56 studies were performed on an mPower scanner (Positron Corporation, Fishers, Indiana) (8). Quantitative phantom studies showed accurate and comparable activity recovery by all scanners. For the University of Texas scanner, 15 to 20 mCi (550 to 750 MBq) of cyclotron-produced N-13 ammonia were used instead of Rb-82, with the last 15 min of the emission images forming the myocardial uptake data. Flow was quantified using our radionuclide-specific model (9).

**ABBREVIATIONS
AND ACRONYMS**

AUC = area under the curve

CAD = coronary artery disease

CFR = coronary flow reserve

CT = computed tomography

ECG = electrocardiogram/electrocardiography

LV = left ventricle/ventricular

PCI = percutaneous coronary intervention

PET = positron emission tomography

PRP = pressure-rate product

ROC = receiver-operator characteristic

Figure 1. LV Quadrants in Cardiac PET

Display of left ventricular (LV) myocardial perfusion by quadrants, as applied to clinical data in later figures. Three-dimensional tomographic data are reoriented into 2-dimensional topographic data and shown by quadrant. PET = positron emission tomography.
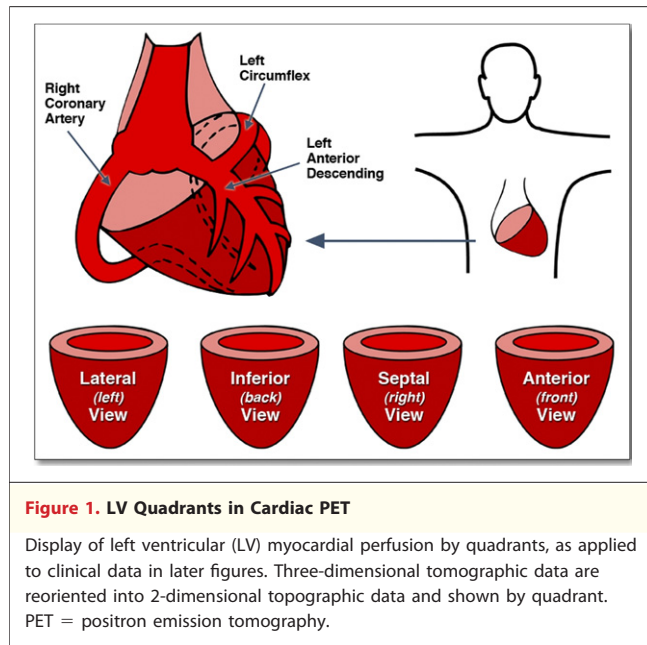
Image reconstruction. Images were reconstructed using filtered backprojection with a ramp filter (cutoff: 6.5 mm), and then processed by a Butterworth filter (cutoff: 0.50 cycles/cm, rolloff: 10 dB/decade). Fused emission and transmission images optimized coregistration by shifting as needed. After reconstruction, a 3-dimensional rotation algorithm generated true short- and long-axis views of the left ventricle (LV) from transaxial images using previously described quantitative software (3–5). Circumferential profiles of maximum LV radial activity for each true short-axis slice were used to construct 2-dimensional topographic views as in Figure 1. Visual display, but not quantitative analysis, utilized bilinear interpolation for figures.

Absolute myocardial flow. Peak integrated activity over an approximate 2×2-mm circular area, typically in the left atrium or thoracic aorta, but occasionally in the central LV cavity, was determined from transaxial images acquired during the first 2 min after each radiotracer injection. Integrated myocardial activity on late images was determined from topographical LV maps. For each radial segment of every short-axis slice, integrated arterial input and integrated myocardial uptake were used to compute absolute myocardial flow using an established model (9) implemented using custom software. Partial volume corrections were based on quantitative phantom studies specific for each scanner (10). The 21-slice (each slice approximately 2.7 to 3.8 mm thick) by 64 radial pixel topographic flow map from Positron and GE scan-

ners was smoothed using a 5×5 pixel average to suppress noise introduced by the flow model. CFR was computed as the stress-to-rest ratio. Worst single pixel flow during dipyridamole stress and worst CFR were recorded by software. As flow is computed on a pixel-by-pixel basis, the worst pixel may be located at different points in rest, stress, and CFR images. Therefore, worst CFR may not represent worst stress flow divided by worst rest flow. Additionally, average CFR may not equal the ratio of average stress to rest flow. Average quadrant flows do not differ significantly in normal volunteers (2).

Quantitative endpoints and classification. Four basal slices were not used for quantitative analysis due to low counts in the membranous interventricular septum. Two apical slices were not used for quantitative analysis due to potential partial volume errors caused by partial thickness slices through the LV apex and apical motion. Combined size and severity of perfusion defects was quantified by percent of the whole topographic image with relative activity less than 60% of maximum activity (100%), which is more than 6 standard deviations below mean activity in normal volunteers (2).

A significant perfusion defect was defined as >2% of the LV below 60% of maximum activity. Myocardial infarction was defined as significant perfusion defects at rest and stress. A stress-induced perfusion defect was defined as a >5% change from the resting scan in the amount of LV below 60% of maximum activity.

Studies were classified into mutually exclusive groups. Definite ischemia was defined as a significant stress-induced perfusion defect and the development of either or both of ST-segment depression >1 mm from baseline during dipyridamole hyperemia or severe angina requiring intravenous aminophylline, sublingual nitroglycerin, and/or intravenous metoprolol for resolution. In patients whose baseline ECG limited interpretation of ST-segment changes (left bundle branch block or ventricular paced rhythm), the ST-segment depression criterion was not used. Indeterminate clinical features were defined as at least 1 of a dipyridamole-induced perfusion defect, significant ST-segment depression, or severe angina requiring intravenous aminophylline, sublingual nitroglycerin, and/or intravenous metoprolol for resolution. Studies without myocardial infarction and without ischemia were classified as nonischemic. Studies with myocardial infarction but no ischemia were classified as having only scar.

A small number of patients with studies at most 40 days before and within 100 days after percutaneous coronary intervention (PCI) were compared to determine the effects of revascularization on absolute flow endpoints, as pilot observations were limited in size by funding.

Systolic blood pressure and heart rate were recorded both at rest and at peak stress imaging. The quantitative perfusion threshold that caused ischemia was normalized to a pressure-rate product (PRP) of 7,000 at rest (equivalent to a standardized heart rate to 70 beats/min and systolic blood pressure of 100 mm Hg) and 10,000 at vasodilator stress (equivalent to a standardized heart rate of 100 beats/min and systolic pressure of 100 mm Hg), based on average values in our cohort. PRP adjustment was performed to explore for any residual relationship between PRP and hyperemia after coronary vasodilation.

Statistical methods. All statistical analyses were performed using R version 2.12 (11) with the ROCR package (12) used to compute receiver-operator characteristic (ROC) curves, sensitivity, specificity, and area under the curve (AUC). Continuous variables are summarized as mean ± standard deviation, or median (interquartile range) for non-normal distributions, and were compared between groups using the t test (or Kruskal-Wallis test for non-normal distributions), which was paired for serial studies in the same patient. Frequency variables are summarized as number (percent) and compared using a chi-square or Fisher exact test. Association between paired and continuous variables is summarized using the square of the Pearson correlation coefficient. Box plots identify outliers as 1.5 times the interquartile range. Worst vasodilator stress flow and worst CFR cutoffs separating groups match sensitivity to specificity. All applicable tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

A total of 1,674 PET studies were performed in 1,370 unique patients. Table 1 lists demographic and clinical characteristics at each study. Studies with ischemia had higher burdens of cardiovascular risk factors, prior mechanical revascularization, or recent clinical angina.

A total of 194 (12%) studies demonstrated definite ischemia (a significant new or worse perfusion defect during dipyridamole plus either or both of significant ST-segment depression or severe angina requiring intravenous aminophylline, sublingual nitroglycerin, and/or intravenous metoprolol for resolution); 301 (18%) studies demonstrated indeterminate clinical features (at least 1 of a dipyridamole-induced defect, significant ST-segment depression, or severe angina); and 339 (20%) studies demonstrated only scar;

Table 1. Baseline Demographics and Clinical Characteristics

	No Ischemia	Indeterminate Clinical Features	p Value	Definite ischemia	p Value
Number of studies	840 (50%)	301 (18%)	N/A	194 (12%)	N/A
Severe angina	0 (0%)	57 (19%)	N/A	150 (77%)	N/A
Stress ST-segment depression	0 (0%)	47 (16%)	N/A	131 (68%)	N/A
Stress-induced defect	0 (0%)	214 (71%)	N/A	194 (100%)	N/A
Rest SBP, mm Hg	116 ± 17	123 ± 18	<0.001	127 ± 18	<0.001
Rest HR, beats/min	61 ± 11	61 ± 12	0.82	62 ± 12	0.24
Stress SBP, mm Hg	118 ± 16	125 ± 18	<0.001	131 ± 21	<0.001
Stress HR, beats/min	90 ± 15	87 ± 15	0.004	87 ± 14	0.005
Age	53 ± 17	62 ± 11	<0.001	64 ± 9	<0.001
Male sex	656 (78%)	242 (80%)	0.46	171 (88%)	0.001
Prior PCI	118 (14%)	111 (37%)	<0.001	51 (26%)	<0.001
Prior CABG	43 (5%)	60 (20%)	<0.001	65 (34%)	<0.001
Recent angina	20 (2%)	37 (12%)	<0.001	73 (38%)	<0.001
Diabetes	63 (8%)	29 (10%)	0.27	11 (6%)	0.44
Current tobacco use	42 (5%)	25 (8%)	0.045	12 (6%)	0.48
Hypertension	334 (40%)	159 (53%)	<0.001	109 (56%)	<0.001
Hyperlipidemia	597 (71%)	253 (84%)	<0.001	165 (85%)	<0.001
Family history of atherosclerosis	576 (69%)	223 (74%)	0.08	149 (77%)	0.024

Values are n (%) or mean ± SD. p values compared to no ischemia versus indeterminate clinical features.
CABG = coronary artery bypass grafting; HR = heart rate; N/A = not applicable; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

whereas 840 (50%) studies demonstrated no ischemia or scar.

The worst vasodilator stress flow was 0.47 ± 0.26 ml/min/g in studies with definite ischemia compared with 1.56 ± 0.54 ml/min/g in studies without ischemia or scar (p < 0.001). The optimal separation between these groups occurred at a vasodilator stress flow cutoff of 0.91 ml/min/g with an AUC = 0.98. The worst CFR was 1.21 ± 0.57 in studies with definite ischemia compared with 2.47 ± 0.77 in studies without ischemia or scar (p < 0.001). The optimal separation between these groups occurred at a CFR cutoff of 1.74 with an AUC = 0.91. In studies with definite ischemia, 77 (40%) had worst CFR <1 (myocardial steal), whereas in studies without ischemia, 12 (1.4%) had worst CFR <1.

Studies with indeterminate clinical features had a worst vasodilator stress flow of 0.81 ± 0.47 ml/min/g (p < 0.001 compared with no ischemia). The optimal separation between these groups occurred at a cutoff of 1.12 ml/min/g with an AUC = 0.86.

The worst CFR was 1.72 ± 0.70 in studies with indeterminate clinical features (p < 0.001 compared with no ischemia). The optimal separation between these groups occurred at a CFR cutoff of 2.03 with an AUC = 0.77. In studies with indeterminate clinical features, 43 (14.3%) had myocardial steal.

The optimal separation between the indeterminate and definite ischemia groups occurred at a worst vasodilator stress flow cutoff of 0.52 ml/min/g with AUC = 0.74 and worst CFR cutoff of 1.36 with AUC = 0.72. The lower AUC for separating the indeterminate from definite ischemia groups is expected from the well-known improvement in diagnostic accuracy from aggregating (as in the definite ischemia group) individual endpoints (as in the indeterminate group).

Figure 2 illustrates rest–dipyridamole PET in the no ischemia, indeterminate, and definite ischemia groups. Figure 3 shows the box plots and cutoff values for these groups along with the optimal cutoff values for worst vasodilator stress flow and
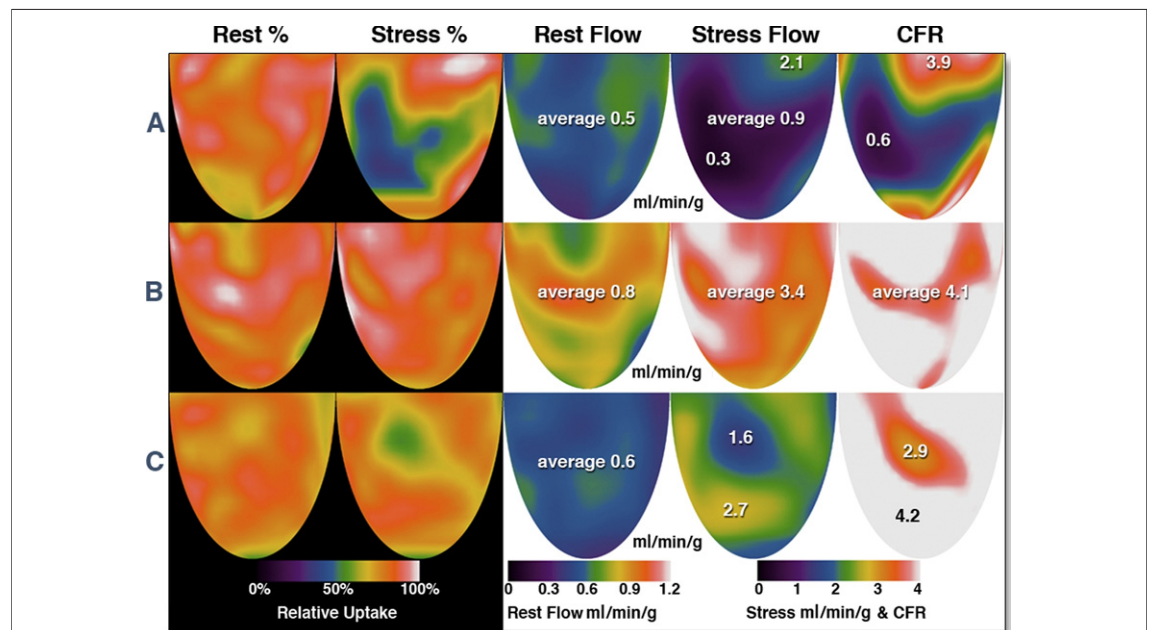

Figure 2. Examples of Clinical Categories of Patients

Although quantitative data were obtained for all quadrants, the positron emission tomography (PET) images show only the significant single view for publication efficiency. **(A)** Definite ischemia. Rest–dipyridamole PET shows a severe, inferior, stress-induced perfusion defect with lowest stress flow of 0.3 ml/min/g and coronary flow reserve (CFR) of 0.6, indicating myocardial steal associated with collaterals to an occluded, dominant left circumflex coronary artery. In the basal inferior area, vasodilator stress flow of 2.1 ml/min/g and CFR of 3.9 are excellent. **(B)** No ischemia with dense coronary calcifications, a coronary arteriogram reportedly showing moderate 3-vessel disease for which bypass surgery was recommended, leading to PET for a second opinion. Rest–dipyridamole PET shows no clinically significant stress-induced perfusion defect with high stress perfusion of 3.4 ml/min/g and CFR of 4.1, indicating excellent flow capacity with diffuse, calcific, nonobstructive coronary atherosclerosis and no flow-limiting stenosis. **(C)** Indeterminate clinical features. Rest–dipyridamole PET shows a moderate, anterior, stress-induced perfusion defect in the distribution of a diagonal but with adequate stress perfusion of 1.6 ml/min/g and adequate CFR of 2.9 in the defect.
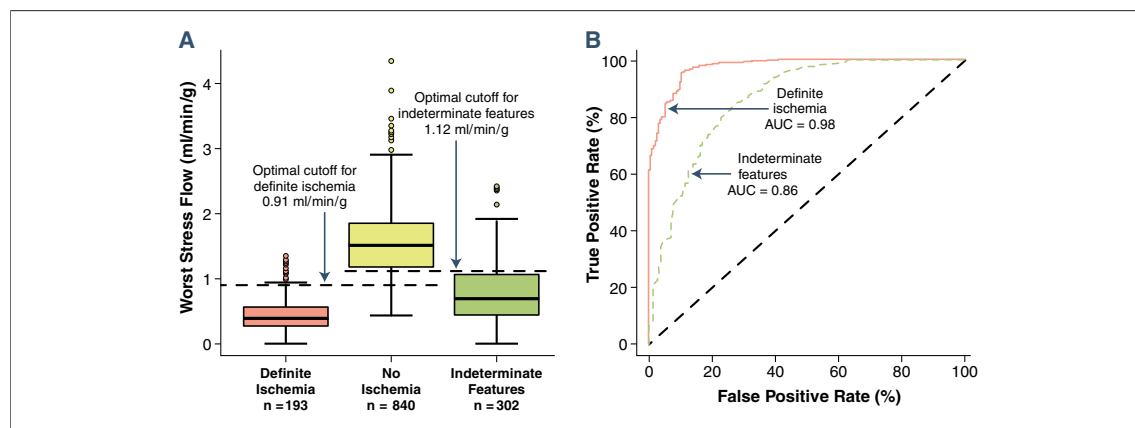
Figure 3. Low-Flow Ischemic Thresholds

Box plot **(A)** and receiver-operator characteristic curves **(B)** for worst myocardial vasodilator stress flow in ml/min/g, for no and definite ischemia groups, and those with indeterminate clinical features along with optimal cutoffs **(thick, dashed black lines)**. AUC = area under the curve.

ROC curves for separating no ischemia from the other groups. Less than 10% (9.8%) of the definite ischemia group had flow above the ischemic threshold of 0.91 ml/min/g. In the group without ischemia, <10% (9.5%) had flows below this threshold. Figure 4 illustrates changes in quantitative PET measurements after PCI. Although quantitative data were obtained for all quadrant views shown in Figure 1, the PET images of Figure 2 and Figure 4 show only the significant single view for publication efficiency.

Average PRP at rest was 7,351 ± 1,869 mm Hg/min and increased to 10,861 ± 2,504 mm Hg/min during peak dipyridamole stress. PRP cor-
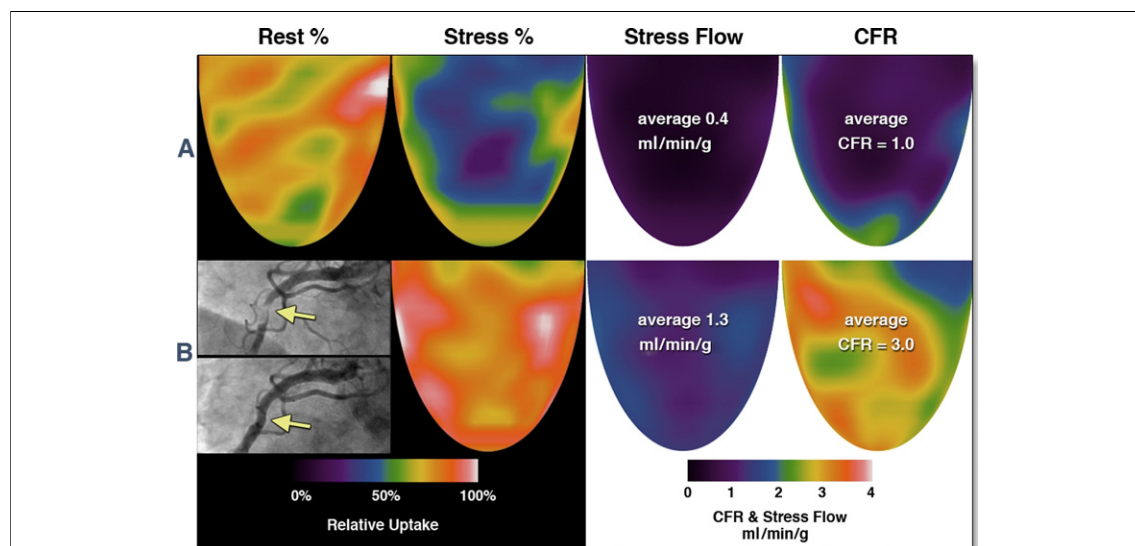

Figure 4. Example of Improvement After PCI

Relative PET perfusion images and quadrant average vasodilator stress flow and CFR before **(A)** and after **(B)** successful percutaneous coronary intervention (PCI) of the proximal right coronary artery. Baseline diagnostic PET was done for recent, mild exertional angina. Rest–dipyridamole PET shows resting perfusion heterogeneity and a severe, inferior, stress-induced defect with average stress flow of 0.4 ml/min/g and CFR of 1.0, with worst stress flow of 0.2 ml/min/g and CFR of 0.5, indicating localized myocardial steal. Angiography showed severe stenosis **(yellow arrow)** with collaterals only from the left system. After successful PCI, average vasodilator stress flow improved to 1.3 ml/min/g and CFR improved to 3.0, with worst vasodilator stress flow of 1.0 ml/min/g and worst CFR of 1.8, indicating resolution of myocardial steal. No medication changes were made between studies. The small **blue region** in the **upper right** of the CFR image is the membranous septum that has no perfusion and is a normal finding. Although quantitative data were obtained for all quadrants, the PET images show only the significant single view for publication efficiency. Abbreviations as in Figures 1 and 2.

related significantly but weakly with whole LV flow, stronger at rest ($r^2 = 0.22$, $p < 0.001$) than during stress ($r^2 = 0.08$, $p < 0.001$), as expected given the uncoupling of coronary flow from metabolic demand with dipyridamole. Therefore, adjusting the worst vasodilator stress flow and CFR to PRP did not improve the AUC by ROC analysis (worst stress flow cutoff: 0.89 ml/min/g at 10,000 PRP, AUC = 0.99; worst CFR cutoff: 1.75 at 10,000/7,000 PRP, AUC = 0.91). Separately analyzing the 2 scanners accounting for over 96% of the studies showed similar results to the whole group.

Of the 302 studies in the indeterminate group, 100 (33%) had worst vasodilator stress flows below the ischemic threshold and reversible defects >10% of the LV, but no severe angina or significant ST-segment changes with dipyridamole. Another 98 (32%) studies had worst vasodilator stress flows below the ischemic threshold but with reversible defects <10% of the LV, roughly evenly split between defects sized <5% and 5% to 10% of the LV. Only 41 (14%) of studies had worst vasodilator stress flows between the 2 nonischemic thresholds, of which only 6 (2%) had reversible defects >10% of the LV. Of the remaining 66 (22%) studies with worst vasodilator stress flows above the ischemic thresholds, only 8 (3%) had reversible defects >10% of the LV.

For pilot data, 12 patients underwent quantitative PET studies before (median: 5 days, interquartile range: 1 to 8 days, maximum: 38 days) and after (median: 17 days, interquartile range: 12 to 27 days, maximum: 96 days) PCI. In the treated territory the average vasodilator stress perfusion increased from 0.98 ± 0.47 to 1.43 ± 0.36 ml/min/g (p = 0.018) and average CFR improved from 1.77 ± 0.99 to 2.79 ± 0.81 (p = 0.005). Severe, dipyridamole-induced angina requiring intravenous aminophylline, sublingual nitroglycerin, and/or intravenous metoprolol for resolution disappeared in all cases after PCI, as did significant ST-segment depression in 3 of 5 cases. Dipyridamole-induced relative perfusion defect severity <60% of maximum decreased from 26% (interquartile range: 16% to 45%) to 5% (interquartile range: 1% to 13%) of the LV (p = 0.009).

DISCUSSION

Regional vasodilator stress flow below 0.91 ml/min/g in dipyridamole-induced PET perfusion defects causes significant ST-segment depression and/or severe angina requiring intravenous amino-phylline, sublingual nitroglycerin, and/or intravenous metoprolol. However, when the worst vasodilator stress flow exceeds 1.12 ml/min/g, these manifestations of ischemia occur rarely. Between 0.91 and 1.12 ml/min/g, angina or ST-segment change may or may not develop. For this narrow intermediate range, the size and severity of relative vasodilator stress-induced defects and surrounding flows indicating the extent of diffuse disease additionally quantify its extent and severity. Average vasodilator stress flow and CFR in myocardial segments supplied by severely stenotic epicardial arteries improve to above these thresholds after successful PCI.

Dipyridamole and other vasodilatory stressors produce fundamentally different stress physiology than exercise. One key difference is disruption of coronary autoregulation by these vasodilators, with resulting potential subendocardial steal distal to flow-limiting stenosis, as well documented experimentally. In addition, exercise-induced coronary vasoconstriction (13) or increased metabolic demand from high heart rate and increased myocardial contractility may alter the ischemic thresholds between exercise and vasodilation. Sympathetic coronary vasoconstriction during exercise, particularly in CAD patients with endothelial dysfunction, and higher perfusion pressure with exercise compared with vasodilator stress may alter coronary flow in complex, unpredictable ways. Therefore, comparing the PRP in the dipyridamole group with that which might be produced during a Bruce stress test is conjecture beyond the scope of our data. However, quantitative perfusion during vasodilator stress offers valid insights into physiological severity of diffuse and segmental disease, perhaps even the optimal measure of severe structural flow limitations independent of numerous physiologic factors that worsen ischemia with exercise in addition to a fixed structural lesion (14). In an individual patient, the lack of definite ischemia during vasodilator stress may not exclude ischemia during exercise stress.

The differential prevalence of recent angina at the bottom of Table 1 (2% for no ischemia, 12% for indeterminate features, and 38% for definite ischemia) suggests an approximate correlation between vasodilator ischemia and exercise ischemia. More frequent angina with vasodilator stress than with exercise may occur, perhaps due to "subendocardial steal," reflected as lowered "average transmural" flow in our data. Additionally, fractional flow reserve is measured during vasodilator stress and not

exercise stress, yet has proven clinical utility despite being a relative coronary flow metric based on surrogate pressure measurements. Thus, vasodilator manifestations of ischemia relate to exercise-induced ischemia, and their potential to guide clinical management requires further study in addition to the basic human physiology reported here.

A low absolute flow and/or CFR can occur both with and without a relative uptake defect as in diffuse disease. Since diffuse coronary disease, commonly associated with all stenoses, does not cause relative perfusion defects, it is essential, not redundant, to include quantitative relative perfusion defects as done here for comprehensive analysis of disease severity needed for management decisions. Our study identifies the low-flow thresholds causing angina or ST-segment changes within dipyridamole-induced perfusion defects. However, absence of angina or ST-segment change does not exclude ischemia at these flow thresholds where "ischemia" may be "silent" or defined in many different ways, such as wall motion changes or lactate production.

In the indeterminate group, simultaneous application of flow thresholds and reversible defect size identifies 3 subgroups. One-third of this group has an ischemic burden large and severe enough to warrant potential mechanical revascularization; one-third have a severe but small ischemic burden that may respond to initial, aggressive medical therapy with PCI as a fall-back option. One-third have adequate flow but a small perfusion defect that arises due to heterogeneity, likely from distal or diffuse disease or microvascular dysfunction (4).

In the no ischemia category, 80 of 840 (9.5%) had a worst stress flow <0.91 ml/min/g. Of these 80 patients, 60 (75%) had a worst CFR >1.74, and 27 (34%) had a worst CFR >2.03. As can be seen, examining worst stress flow and CFR together reveals that a large number of patients without any clinical manifestations of ischemia (no vasodilator-induced PET defect with no significant ECG changes or severe angina during dipyridamole) who have a worst stress flow below the cutoff <0.91 ml/min/g have relatively intact worst CFR >1.74 to 2.03. Using worst stress flow alone would therefore give a less complete picture of the coronary physiology.

Comparison to existing literature. In a cohort of 26 patients pre-selected and actively undergoing PCI (15), absolute myocardial perfusion was measured using myocardial contrast echocardiography. Ischemia was defined by intracoronary ECG as ST-segment elevation ≥1 mm at the end of a 1-min balloon occlusion of the coronary artery. ROC analysis identified a flow cutoff of 0.37 ml/min/g during coronary occlusion with an AUC = 0.99, comparable to our AUC values from a larger number of patients with a broader spectrum of CAD. The lower flow threshold in this small population likely relates to different flow-measuring methods, exclusive selection of patients scheduled for PCI, and intracoronary ECG changes occurring earlier than clinical angina during the ischemic cascade (16).

Invasive studies using Doppler velocity CFR from 10 studies in a total of 816 patients found optimal cutoffs from 1.7 to 2.1 with AUC = 0.65 to 0.85 (17) when compared with noninvasive functional imaging. These values agree with our noninvasive CFR threshold of 1.74 with AUC = 0.91 for definite ischemia. However, our work extends these prior results by providing a noninvasive absolute flow threshold for ischemia, in addition to a CFR ischemic threshold, derived from a much larger cohort than all of these studies combined.

Study limitations. Cardiac PET quantifies average transmural flow and can distinguish subendocardial from subepicardial perfusion only under conditions of marked hypertrophy. During vasodilation, subendocardial flow may be worse than subepicardial flow, but our transmural average flow thresholds reflect whatever composite flow causes angina or ST-segment change within the dipyridamole-induced perfusion defect.

The myocardial supply/demand balance is affected by numerous factors such as ventricular wall stress, blood pressure-heart rate product, myocardial contractility, ischemic conditioning, individual angina perception threshold, and autonomic dysfunction with aging and diabetes, adding biological variability to our data. Therefore, Figure 3 reflects this biological variability, not the error range of a diagnostic test compared with some other "gold standard" for which ROC analysis is commonly used. Moreover, biological variation in flow thresholds for ischemia would reduce observed differences among groups. Data analysis after removing diabetic patients (n = 169, 10%), who might not experience angina, showed almost identical cutoffs for definite ischemia (0.92 ml/min/g with AUC = 0.98) and indeterminate clinical features ischemia (1.15 ml/min/g with AUC = 0.86) as for the entire group. The lack of improvement in AUC after adjusting for PRP suggests that myocardial demand has minimal differential impact, due both to the relatively uniform PRP during dipyridamole in our cohort and the minimal residual coupling between flow and PRP during stress.

Submaximal vasodilation by dipyridamole, compared with intravenous adenosine or intracoronary papaverine, would reduce the separation between no and definite ischemia groups. Our finding of an AUC = 0.98 for worst vasodilator stress flow suggests that this was not a significant limitation. Definite ischemia required a stress-induced uptake defect >5% in the amount of LV <60% of relative maximum activity. Additionally, a 5 × 5 smoothing filter was applied before finding worst flow in a pixel 2.7 to 3.8 mm thick. Therefore, our flow thresholds involve substantial amounts of myocardium, not random pixel variability distinct from surrounding flow.

CONCLUSIONS

We quantified absolute flow in 1,674 PET studies. Definite ischemia was defined as a dipyridamole-induced perfusion defect with either significant ST-segment depression and/or severe angina requiring treatment. A vasodilator stress perfusion threshold of 0.91 ml/min/g optimally separated definite from no ischemia with an AUC of 0.98 and a CFR cutoff of 1.74 with an AUC = 0.91, reflecting excellent discrimination at the exact moment of definite ischemia. As pilot data, average vasodilator stress flow and CFR improved to substantially above ischemic thresholds after successful PCI. The application of the physiological observations from our data will require further extended study before understanding their clinical relevance. Our observations suggest quantitative myocardial perfusion may be appropriate for a clinical trial of managing suspected or established CAD.

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