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Flow-Function Relation in Patients With Chronic Coronary Artery Disease and Reduced Regional Function

A Positron Emission Tomographic and Two-Dimensional Echocardiographic Study With Coronary Vasodilator Stress

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Objectives. **We sought to elucidate the flow-function relation in chronic postischemic dysfunction during vasodilator stress.**

Background. **In patients with ischemia and regional dysfunction, stress echocardiography can elicit three responses in the dysfunctioning segments: no change, improvement or worsening. The physiology underlying these responses is unclear.**

Methods. **Seventeen patients with ischemia and left ventricular dysfunction underwent evaluation of regional function by two-dimensional echocardiography and myocardial blood flow by positron emission tomography and ^{13}N-ammonia. Flow (ml/min per g) and function (regional wall motion score [RWMS] from 1 = normal to 4 = dyskinetic) were evaluated both at rest and after dipyridamole (0.56 mg/kg body weight over 4 min).**

Results. **In 45 normal segments, rest to dipyridamole flow increased from 0.83 ± 0.22 (mean ± 1 SD) to 1.87 ± 0.90 ($p < 0.01$) with a hyperkinetic contraction pattern. Among dysfunctioning segments, responders (n = 11) showed an upsloping flow-function curve during stress (i.e., increased function [RWMS rest 2.5 ± 0.5 vs. dipyridamole 1.2 ± 0.4] and increased flow [rest 0.69 ± 0.30 vs. dipyridamole 1.89 ± 1.43, $p < 0.01$]); nonresponders (n = 20) had a flat flow-function curve during dipyridamole (i.e., fixed function [RWMS rest and dipyridamole 2.6 ± 0.5] and no flow increase [rest 0.64 ± 0.24 vs. dipyridamole 0.87 ± 0.51, p = NS]): Ischemic segments (n = 9) exhibited a downsloping flow-function curve during dipyridamole (i.e., worsened function [RWMS rest 2 ± 0.5, dipyridamole 3.1 ± 0.6] and no significant flow change [rest 0.67 ± 0.29 vs. dipyridamole 0.79 ± 0.23, p = NS]).**

Conclusions. **Myocardial segments with rest dysfunction and a contractile reserve elicitable by a vasodilator stress more often exhibit residual flow reserve, whereas segments with a fixed or worsening mechanical response during stress show a flat flow response.**

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In patients with chronic coronary artery disease and reduced regional function, pharmacologic stress echocardiography can elicit three distinct responses in the basally dysfunctioning segment: no change ("necrotic" pattern); improvement in function ("viable" pattern); worsening in function ("ischemic" pattern) (1).

The physiology underlying these responses is, however, unclear and largely hypothetical (2), although it has been speculated that during chronic ischemia there is a rightward shift of the normal flow-function curve, with a greater reduction in function occurring for any given reduction of flow (3). In a previous study, we (4) assessed the relation during coronary vasodilator stress between regional wall motion and coronary flow reserve in patients with single-vessel disease and no myocardial infarction. However, no data on flow-function correlation during coronary vasodilation are available in patients with chronic coronary artery disease and reduced regional function. Such data are crucial to understanding clinical findings in the context of defined pathophysiologic principles, since it is widely accepted that medicine without physiology is merely phenomenology (3). The present study was designed to assess the flow-function correlates during coronary vasodilator stress of 17 patients with chronic coronary artery disease and reduced regional function. Regional function was evaluated by two-dimensional echocardiography, and regional flow by positron emission tomography (PET) and ^{13}N-ammonia,

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Abbreviations and Acronyms

ECG = electrocardiogram, electrocardiographic
PET = positron emission tomography (tomographic)
RWMS = regional wall motion score

matched on a segment by segment basis, both at rest and after a low dose (0.56 mg/kg over 4 min) dipyridamole stress.

Methods

Study patients. We studied 17 patients (13 men, 4 women, mean age ± SD 59 ± 7 years) with a history of chest pain with myocardial ischemia documented by electrocardiogram (ECG), or previous myocardial infarction, or both. Eleven of these patients were included in a previous study (5) (that did not include stress echocardiography data) on the relation between myocardial flow reserve and viability. As inclusion criteria, all patients had regional left ventricular dysfunction at rest. Exclusion criteria were unstable angina (making discontinuation of therapy unethical), left ventricular hypertrophy, valvular heart disease, diabetes mellitus (which may alter coronary flow response independent of coronary artery disease), asthma and obstructive pulmonary disease (which represent a relative contraindication to dipyridamole stress) or technically inadequate acoustic window (which precludes evaluation of left ventricular function by the echocardiographic technique). In all patients, coronary angiography documented significant coronary artery disease: single-vessel in 14 patients, double-vessel in 2 and triple-vessel in 1 patient. All patients were studied in the absence of antianginal therapy in random order and on different days. Within 2 weeks, each patient had undergone baseline echocardiography, dipyridamole stress echocardiography and a coronary flow reserve study by PET. Caffeine and theophylline derivatives were withheld at least 12 h before dipyridamole tests to prevent interference with the hyperemic effect of dipyridamole.

Baseline echocardiographic examination. Two-dimensional echocardiograms were obtained by using commercially available imaging systems. Echocardiographic images were digitally acquired as well as recorded on videotape for subsequent playback and analysis. According to the recommendations of the American Society of Echocardiography (6), segmental wall motion was semiquantitatively graded as follows: 1 = normal; 0 = hyperkinetic, increased endocardial motion and thickening; 2 = hypokinetic, marked reduction of endocardial motion and thickening; 3 = akinetic, virtual absence of inward motion and thickening; and 4 = dyskinetic, paradoxic wall motion away from the center of the left ventricle in systole. Regional wall motion score (RWMS) was individually calculated for each segment. Inadequately visualized segments (i.e., without complete endocardial delineation) were not scored. To reconcile the 16-segment model proposed by the American Society of Echocardiography (6) and generally adopted in stress echocardiography with the limited spatial resolution of PET imaging, we considered only three regions—anterior septum, anterior wall and posterolateral wall—according to the 11-segment model of the left ventricle previously adopted in correlative studies on two-dimensional echocardiography with PET (4). Each region was divided into three segments: proximal, middle and apical.

Low dose dipyridamole stress echocardiographic test. Two-dimensional echocardiography and 12-lead ECG monitoring were performed in combination with dipyridamole infusion (0.56 mg/kg body weight over 4 min) (7). In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the procedure, the blood pressure and the ECG were recorded each minute. The videotapes were analyzed by a cardiologist-echocardiographer who had no knowledge of the clinical, angiographic or scintigraphic data. The low level of intraobserver and interobserver variability between experienced observers in our laboratory has been documented (8) and is probably linked to previous extensive experience in joint reading and development of a priori reading criteria, thus overcoming the otherwise more substantial variability among independent expert readers (9). A digital acquisition of images of interest was obtained with a side by side display of rest and peak stress images in a cine-loop mode, either on-line or off-line by an array processor–based computer for medical image processing (Mipron, Kontron). RWMS was derived for rest and peak stress (0 to 1 min after the end of infusion) echocardiograms in every segment in each patient, as previously described for the baseline echocardiographic examination. Each analyzed segment could belong to only one of the following predefined subsets: 1) *normal* (RWMS rest = 1; RWMS dipyridamole = 1); 2) *ischemic* or *worsening* (RWMS rest ≥1; RWMS dipyridamole > rest); 3) *responder* (RWMS rest >1; RWMS dipyridamole < rest); 4) *nonresponder* or *fixed* (RWMS rest >1; RWMS dipyridamole = rest).

Regional myocardial blood flow study. We used a two-ring positron tomograph (ECAT III, Siemens/CTI) that provides three simultaneous cross sections of the heart (two from the primary planes and one from the interplane). Regional myocardial blood flow was assessed with ^{13}N-ammonia. Tracer (15 to 20 mCi) was infused as a slow bolus over 10 to 20 s. Dynamic tomographic data acquisition started simultaneously, as previously described (10). After acquisition of the baseline study, a period of 50 min was allowed for the physical decay of ^{13}N-ammonia. Thereafter, dipyridamole (0.56 mg/kg in 4 min) was infused intravenously under continuous ECG monitoring. The second injection of ^{13}N-ammonia was started 2 to 3 min after the end of dipyridamole infusion and the dynamic tomographic data acquisition followed the same protocol as that of the baseline study. To antagonize the effects of dipyridamole, aminophylline (120 to 240 mg) was injected 3 min after the dipyridamole ^{13}N-ammonia injection in all patients. In each patient, the two planes that better represented the left ventricular walls were analyzed. Each tomographic plane was divided into three regions: septal, anterior and posterolateral.

Table 1. Clinical, Echocardiographic and Angiographic Features of the Study Patients

Pt No.	Age (yr)/ Gender	Prev MI	Coronary Angiography (% stenosis)			EF (%)
			LAD	LCx	RCA	
1	55/M	Non-Q	100	0	0	40
2	62/F	Q	0	90	0	44
3	68/M	Q	100	0	0	48
4	57/M	Q	100	0	0	45
5	58/M	Q	95	0	0	46
6	65/M	Q	100	0	0	39
7	61/F	Q	99	90	75	29
8	58/M	Non-Q	0	75	0	53
9	56/M	Non-Q	0	80	0	38
10	70/M	Non-Q	100	0	0	51
11	52/M	Q	100	0	0	52
12	51/M	None	90	0	0	56
13	45/F	None	90	0	0	54
14	67/F	Non-Q	100	0	0	45
15	65/M	Q	100	0	0	55
16	63/M	Q	75	100	0	24
17	54/M	Q	75	0	75	50

EF = ejection fraction; F = female; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; M = male; Prev MI = previous myocardial infarction; Pt = patient; Q = Q wave; RCA = right coronary artery.

Images were analyzed by using circumferential profiles. The program normalized ^{13}N-ammonia counts within each myocardial segment to the maximal activity. Segment activity was then expressed as percent of maximal myocardial activity. A group of segments remote from the infarct zone that had normal wall motion by echocardiography and a normal feeding coronary artery served as reference for control segmental ^{13}N-ammonia uptake. Absolute myocardial blood flow was computed according to a method previously validated in our laboratory (10) and described elsewhere (4). The absolute value of myocardial blood flow was expressed as ml/min per g. Coronary reserve was calculated as the ratio between dipyridamole and baseline coronary blood flow.

Statistical analysis. A preliminary analysis was performed to determine if a segment by segment analysis of the data was appropriate in the absence of any consistent intrapatient correlations of the segment data. A total of 72 possible correlations between the 85 left ventricular segments were examined at rest and after dipyridamole infusion for perfusion and echocardiography. Because there were no consistent correlations ($p \geq 0.05$), the segment was used as the unit of analysis. Values are expressed as mean value ± SD. Intergroup comparisons were performed by paired *t* test. Multiple group comparisons (per-segment analysis) were performed with analysis of variance, and the Newman-Keuls test for individual comparisons between groups was applied. A p value < 0.05 was considered statistically significant.

Table 2. Hemodynamic Changes During Stress Echocardiographic Testing

	Baseline	Dipyridamole
SBP (mm Hg)	135 ± 19	141 ± 25
DBP (mm Hg)	82 ± 7	84 ± 9
HR (beats/min)	68 ± 15	88 ± 18*
RPP (mm Hg·beats/min)	9,213 ± 2,534	12,623 ± 4,636*

*$p < 0.05$ versus baseline. Data are expressed as mean value ± SD. DBP = diastolic blood pressure; HR = heart rate; RPP = rate-pressure product; SBP = systolic blood pressure.

Results

Individual demographic, rest echocardiographic and angiographic data of the study patients are summarized in Table 1. Because nine PET segments were obtained for each of the 17 patients studied, the maximal theoretic number of analyzable segments should total 153. However, because only the best two of the three planes obtainable by PET were analyzed, the maximal theoretic number of interpretable segments was only 102. Of these 102 segments, 16 were excluded because suboptimal echocardiographic imaging, precluded reliable assessment of the regional wall motion. Of the remaining 86 segments, 40 were dyssynergic and 46 normal at baseline echocardiography. In one normal segment, a new dyssynergy developed during low dose dipyridamole infusion in a region with normal rest function fed by a critically stenosed coronary artery. This segment was excluded from the analysis of flow data. Therefore, we included in the data analysis the 40 dyssynergic and 45 normal control segments.

Baseline echocardiography. By inclusion criteria, all patients had regional dyssynergy in the rest echocardiogram. Mean ejection fraction (by contrast ventriculography, area-length method) was 0.44 ± 0.1. Among the 40 segments with baseline dyssynergy, 18 were akinetic and 22 hypokinetic.

Stress echocardiography. The systemic hemodynamic response to dipyridamole infusion is reported in Table 2. There was only a slight increase in heart rate, leading to an ~30% increase in rate-pressure product from baseline. Of the 85 considered segments, 45 showed a normal, 9 an ischemic, 11 a responder, and 20 a nonresponder pattern, as previously defined. Nine segments that were hypokinetic in rest basal conditions worsened during low dose dipyridamole infusion.

Myocardial blood flow. The 40 segments with baseline dyssynergy had an average flow of 0.66 ± 0.27 ml/min per g at rest and 1.13 ± 0.93 ml/min per g after dipyridamole ($p < 0.01$). The 45 segments with normal baseline function had a mean rest flow of 0.83 ± 0.22 ml/min per g and 1.87 ± 0.90 ml/min per g after dipyridamole ($p < 0.01$) (Table 3).

Correlation between stress echocardiographic and PET findings. To build a flow-function relation during vasodilator stress in the four described functional patterns, the flow behavior of all segments included in the analysis was assessed. Normal segments had a coronary flow reserve of 2.30 ± 1.15. The corresponding functional pattern was a normal contraction becoming hyperkinetic during stress (Fig. 1). The nine

Table 3. Regional Myocardial Blood Flow at Baseline and During Dipyridamole

	Normal Segments (n = 45)	Basally Dyssynergic Segments		
		Responder (n = 11)	Ischemic (n = 9)	Nonresponder (n = 20)
Baseline (ml/min per g)	0.83 ± 0.22	0.69 ± 0.3	0.67 ± 0.29	0.64 ± 0.24
Dipyridamole (ml/min per g)	1.87 ± 0.90	1.89 ± 1.43	0.79 ± 0.23	0.87 ± 0.51
p value	< 0.01	< 0.01	NS	NS

Data are expressed as mean value ± SD.

Table 4. Regional Myocardial Wall Motion Score at Baseline and During Dipyridamole

	Normal Segments (n = 45)	Basally Dyssynergic Segments		
		Responder (n = 11)	Ischemic (n = 9)	Nonresponder (n = 20)
Baseline	1	2.5 ± 0.5	2 ± 0.5	2.6 ± 0.5
Dipyridamole	0	1.2 ± 0.4	3.1 ± 0.6	2.6 ± 0.5
p value	< 0.01	< 0.01	< 0.01	NS

Data are expressed as mean value ± SD.

ischemic segments, with rest dysfunction, had a rest flow that did not change after dipyridamole (Table 3), yielding a coronary flow reserve of 1.37 ± 0.60 ($p < 0.01$ vs. normal segments). These segments showed a downsloping flow-function curve during stress (Fig. 1), with worsening of function (Table 4) and no increase in flow. In segments with abnormal rest function and no ischemia elicited by dipyridamole infusion, rest regional wall motion score was 2.5 ± 0.5 in responders and 2.6 ± 0.5 in nonresponders (Table 4). Rest flow also was similar in responders and nonresponder segments (Table 3), whereas the peak dipyridamole flow was significantly higher ($p < 0.01$) in responders than in nonresponders (Table 3). Coronary flow reserve was significantly higher in responders than in nonresponders (2.85 ± 2.25 vs. 1.36 ± 0.64, $p < 0.01$). Segments with a responder pattern showed an upsloping flow-function curve during stress (Fig. 1), with increased flow (Table 3) and function (Table 4) after dipyridamole. Segments with a nonresponder pattern showed a flat flow-function curve during stress (Fig. 1), with no significant change in either flow or function after dipyridamole (Tables 3 and 4).

Discussion

A spectrum of mechanical and flow responses after coronary vasodilation can be associated with a similar level of absolute regional rest flow and reduced rest function. Myocardial segments with rest dysfunction and a contractile reserve elicitable by a vasodilator stress more often exhibit a residual flow reserve, whereas segments with a fixed or a worsening mechanical response during stress show a flat flow response.

Flow-function relation during vasodilator stress. The integrated assessment of regional function by two-dimensional echocardiography and regional flow measurement by PET allowed identification of four flow-function patterns, associated with distinct pathophysiologic responses: normal, ischemic, viable and necrotic.

In the *normal segments*, a normal/hyperkinetic contraction pattern was associated with a 250% increase in regional flow. This upsloping flow-function curve (Fig. 1) was characterized by an increase in function with a more substantial increase in flow. Previous studies (11,12) have shown that only a modest inotropic effect on regional and global left ventricular function is detectable with dipyridamole infusion, consistent with the established physiologic finding that functional performance increases with higher than normal perfusion levels, but whatever the increase in flow—up to two to four times rest values—the thickening does not increase by >50% (2,3,13).

In the *ischemic segments*, a worsening of regional function was associated with no significant increase in regional flow. This downsloping flow-function curve (Fig. 1) was characterized by a further worsening of baseline function with almost no increase in flow. This finding is also consistent with experimental and clinical data. In the presence of coronary stenosis, the administration of a coronary vasodilator can induce a true imbalance between supply and demand, as blood flow in the distribution of a coronary artery actually decreases as a result of a "steal" phenomenon (14). On average, in the ischemic segments of our patients, blood flow did not decrease, a finding

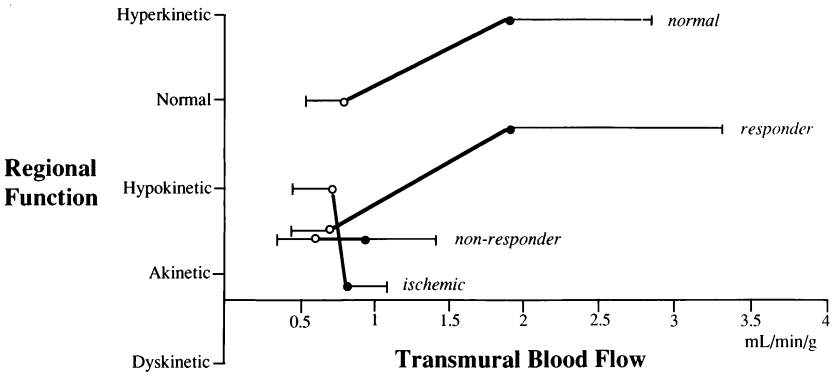

Figure 1. Flow-function relation in patients with chronic coronary artery disease and reduced regional function. Regional transmural blood flow (x-axis) was measured by PET; RWMS (y-axis) was measured semiquantitatively by two-dimensional echocardiography, ranging from dyskinesia up to normal and hyperkinesia. Segments with reduced rest function show fairly similar values of rest flow **(open circles)** but obviously different patterns during vasodilator stress **(closed circles)**: upsloping response in responders; flat response in nonresponders; downsloping response in ischemic segments. Values are expressed as mean value **(circles)** ± 1 SD **(bars)**.

consistent with a transmural or vertical steal, with subepicardial overperfusion in the presence of an absolute reduction in subendocardial flow (15). The expected physiologic consequence of this mechanism is a flat blood flow response, because PET measurement, due to inherent limitations in axial sampling capability and spatial resolution, averages out a reduction in subendocardial and an increase in subepicardial flow (16). Overall regional function is reduced, because the subendocardial layer contributes to 67% of regional thickening, whereas normally there is only a small contribution of the subepicardium to overall thickening (17). We (4) previously observed the blunted flow response in segments becoming ischemic during stress in patients with single-vessel disease and normal rest function who were also studied by two-dimensional echocardiography and PET during vasodilator stress. In that study, we found that dipyridamole-induced regional dysfunction is associated with a reduction in coronary flow reserve that is more severe when the dipyridamole-induced dyssynergy appears earlier during the test. We labeled segments with stress-induced worsening of function as ischemic to differentiate their mechanical response from that of responders. In reality, segments with worsening function during stress are potentially viable and capable of recovering function after revascularization.

In the *viable segments*, an increase in regional coronary flow was mirrored by an increase in function of a segment with baseline dyssynergy. This upsloping flow-function curve (Fig. 1) was characterized by an increase in function and flow. In contrast to the upsloping pattern of normal segments, however, the flow-function curve was shifted rightward; that is, for any given flow the function was depressed, both at baseline and during stress. The possibility of recruiting flow reserve in a segment with rest dysfunction may appear paradoxic, but its occurrence has been clearly shown in experimental (18–20) and clinical (5,21) studies. Residual flow reserve has been documented in patients with severe coronary stenosis and depressed baseline flow in studies employing either left ventricular injection of albumin microspheres (21) or ^{13}N-ammonia (5) as a flow tracer and either papaverine (21) or dipyridamole (5) as a pharmacologic stimulus. This increase in flow is associated with an increase in function through either a hemodynamic effect of increased flow (Gregg effect [22,23]) or a flow-independent direct cardioprotective effect of endogenous adenosine accumulation (24).

In the *necrotic segments*, rest dysfunction remained unchanged after vasodilator stress, with no flow or function response. This flat flow-function curve (Fig. 1) was characterized by no significant change in either flow or function during stress. The likely physiologic correlate of this response is scar tissue. Connective tissue replaces subendocardial or transmural myocytes, preventing contractile response, and the coronary microvascular bed, blunting the flow response.

Comparison with previous studies. The functional response to dipyridamole of basally dysfunctioning segments has been correlated with functional recovery after coronary revascularization and thallium uptake (25,26). Dipyridamole-induced functional recovery shows the same accuracy, with a slightly lower sensitivity and slightly higher specificity, than dobutamine-echocardiography for predicting spontaneously occurring functional recovery after acute myocardial infarction (27). Only one previous study (28) provided a simultaneous assessment of regional wall motion and myocardial perfusion, the latter evaluated by contrast echocardiography. In that study, Rovai et al. showed that residual contractile reserve of asynergic, infarcted segments is associated with either basally preserved myocardial perfusion or decreased perfusion defect by low dose dipyridamole. The present study confirms and expands that previous observation, establishing in more quantitative terms the relation between myocardial perfusion and contractile response in viable myocardium. In fact, myocardial contrast echocardiography provides only an index of myocardial perfusion and to date does not allow the quantitative assessment of myocardial absolute flow (29) that was obtained in the present study by PET imaging (16).

Limitations of the study. We adopted one dose regimen (the standard 0.56 mg/kg over 4 min) for both PET and two-dimensional echocardiographic studies. This dosage was originally proposed by Gould (30) and adopted in first-generation dipyridamole stress echocardiography (7); these stress studies later used high dose dipyridamole (31) and are currently performed with coadministration of atropine (32). The standard dose cannot guarantee maximal coronary vasodilation in all patients and is not ideal for the diagnostic use of stress echocardiography, which requires a higher dose to increase sensitivity (31) and a lower dose to selectively explore myocardial viability without inducing ischemia (26). However, the aim of our study was to establish the flow-function correlates during a given vasodilator stimulus; therefore, we chose the standard dose as a convenient trade-off, offering an adequate hyperemic stress associated with the full spectrum of mechanical responses, from worsening to improvement (33).

The coronary flow and myocardial function studies were performed on separate days. Ideally, simultaneous assessment would have been preferred. Practically, it was impossible to reconcile the need for optimal echocardiographic imaging (usually performed in the left lateral decubitus position) and the need for optimal PET imaging (in the supine position into the gantry). Because dipyridamole stress has high short-term reproducibility (31), this limitation should have not affected the study results to any significant extent.

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