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# Effects of Pharmacologic Coronary Hyperemia on Echocardiographic Left Ventricular Function in Patients With Single Vessel Coronary Artery Disease

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**To assess whether pharmacologic coronary vasodilation could provoke new left ventricular wall motion abnormalities in patients with single vessel coronary artery disease, systemic hemodynamics, coronary blood flow velocity and left ventricular wall motion were measured by two-dimensional echocardiography during administration of 10 mg of intracoronary papaverine in 14 patients before and again immediately after left coronary angioplasty (group 1). As a comparison with an intravenous method, left ventricular wall motion was analyzed after 0.56 mg/kg body weight of intravenous dipyridamole in a separate group of 13 patients with single vessel coronary disease (group 2). Heart rate-blood pressure product increased 3% to 6% in papaverine-treated patients and 14 ± 11% (p = NS) in dipyridamole-treated patients. No angiographic collateral vessels were present in either group.**

**Although intracoronary mean flow velocity measured in the 14 group 1 patients and in 5 normal control subjects during papaverine treatment increased from 125% to 400% of basal flow velocity, papaverine induced new left ventricular wall motion abnormalities in only 5 of the 14 patients before coronary angioplasty. In three of five patients, left ventricular wall motion abnormalities persisted after successful coronary angioplasty. Four of the 14 patients demonstrated augmentation of left ventricular wall motion with papaverine. After intravenous dipyridamole, only 3 of the 13 group 2 patients developed new left ventricular regional asynergy.**

**These data suggest that selective (papaverine) and, most likely, global (dipyridamole) augmentation of coronary flow alone does not reliably identify potential ischemic left ventricular regions affected by critical single vessel coronary artery disease.**

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Coronary vasodilators may provoke new left ventricular wall motion abnormalities in regions supplied by stenotic coronary arteries. Dipyridamole-induced coronary hyperemia with echocardiographic assessment of left ventricular wall motion has been demonstrated as a feasible and reliable provocative test for myocardial ischemia in patients with coronary artery disease (1–3). Pharmacologic coronary hyperemia can induce new asynergy in a region supplied by critical coronary stenosis in some patients, whereas in others, myocardial regions supplied by coronary arteries with similar or nearly identical angiographic narrowings may demonstrate either normal or hypocontractile response patterns (1). The differences in left ventricular functional responses among these patients have been attributed to different degrees of coronary vasodilator reserve (1,4–6).

The mechanisms by which coronary hyperemia induces regional asynergy in patients with single vessel coronary artery disease are under study, but may include a transmural coronary steal with preferential redistribution of subendocardial to subepicardial perfusion. The increase in the transstenotic pressure gradient as a consequence of the increase in coronary flow may produce a decrease in distal perfusion with subendocardial ischemia and left ventricular dysfunction (6). This hypothesis was supported, in part, by studies (1) measuring great cardiac vein efflux during dipyridamole-

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induced hyperemia. However, in the particular patient subgroup of Picano et al. (1), angiographic collateral vessels were observed frequently in patients with dipyridamole-induced left ventricular wall motion abnormalities. Patients with coronary collateral vessels and isolated left anterior descending artery stenosis had impaired left ventricular wall motion, suggesting a different mechanism possibly involving a regional coronary "steal" of blood away from collaterally supplied regions.

The purpose of this study was to examine selective coronary hyperemia and regional asynergy, testing whether intracoronary papaverine-induced hyperemia would result in left ventricular wall motion abnormalities similar to those observed with intravenous dipyridamole. If significant and consistent results were obtained in a subset of patients with isolated single vessel coronary artery disease, intracoronary selective hyperemia would prove to be a clinical laboratory tool useful for identifying physiologically significant coronary artery narrowings.

## Methods

**Study patients.** The study group consisted of 32 patients. Fourteen patients (group 1) with a single stenotic coronary artery underwent diagnostic coronary angiography and subsequent left anterior descending artery (n = 11) or circumflex artery (n = 3) angioplasty for anginal chest pain. As a comparison with coronary vasodilation with intravenous dipyridamole and two-dimensional echocardiographic assessment (3), 13 patients (group 2) with angiographic single vessel coronary disease (left anterior descending artery, n = 11; circumflex artery, n = 2) were retrospectively reviewed with regard to dipyridamole-echocardiographic left ventricular functional response before coronary angioplasty. Left ventricular functional data were unavailable after coronary angioplasty in this subgroup. Three patients in group 1 had regional akinesia and one patient in group 2 had severe inferior hypokinesia by echocardiography during rest conditions. No patient had angiographic collateral supply to the region of study. Patients with uncontrolled hypertension, valvular disease or evidence of severe left ventricular hypertrophy by echocardiography were excluded. Five of the 32 patients having no or minimal coronary artery disease were studied as a control group after diagnostic catheterization for chest pain syndromes. All medications were continued as prescribed by the physician. All subjects gave written informed consent to the protocol, which was approved by the Human Subjects Research Committee of St. Louis University.

**Cardiac catheterization.** For group 1 and the normal group, diagnostic cardiac catheterization was performed in a fasting state. Premedication included diphenhydramine (25 to 50 mg) and diazepam (2 to 5 mg). Suitable patients with single vessel coronary artery disease were then referred for coronary angioplasty at a separate procedure. Biplane left ventriculography was performed when available. Multiple projections of coronary angiograms were obtained in appropriate angled views in all patients. Angiograms were visually reviewed by two independent experienced observers. Coronary artery disease was defined as >60% diameter narrowing in major epicardial vessels. In patients with normal coronary arteries, the evaluation of pharmacologic coronary hyperemia and left ventricular function was performed >15 min after the last radiographic contrast injection.

**Intracoronary papaverine/echocardiographic study.** In the catheterization laboratory, baseline echocardiographic left ventricular wall motion was studied by standard two-dimensional echocardiographic technique with appropriate views continuously obtained before, during and for 3 min after bolus injection of 10 mg of papaverine into the left coronary artery. A commercially available, wide angle, phased array imaging system (Hewlett-Packard model 77020) with 3.5 and 5.0 MHz transducers was used. In baseline studies, standard echocardiographic views (long-axis, short-axis and apical two and four chamber) were obtained.

*Videotapes were analyzed without prior knowledge of cardiac catheterization findings.* During coronary hyperemia, new areas of abnormal left ventricular wall motion were identified and qualitatively assessed, as previously reported (3). Left ventricular regional wall motion was graded as hyperkinetic, normal, hypokinetic, akinetic or dyskinetic.

**Intracoronary Doppler flow velocity measurements.** In 19 patients (group 1 and normal group), intracoronary arterial flow velocity was measured at rest and during maximal papaverine-induced coronary hyperemia. An 8F Judkins coronary guiding catheter (USCI or Shiley, Inc.) was positioned in the ostium of the left coronary artery. The catheter position was adjusted to avoid pressure damping. Intracoronary velocity was measured with a 2.5F Doppler catheter (Millar Instruments) with a 20 MHz pulsed Doppler crystal, as previously described (7,8). After the diagnostic study, the intracoronary velocity catheter was then inserted over a 300 cm long, 0.014 in. (0.04 cm) guide wire through an 8F guiding coronary catheter. In the 14 patients undergoing coronary angioplasty (group 1), 10,000 U of heparin was given before guide wire insertion (in the normal group, 3,000 U of heparin was given). In the five normal patients, the Doppler catheter was advanced <1 cm proximal to the lesion or to the mid or proximal portion of the left anterior descending or circumflex artery. This location was recorded on videotape for catheter replacement after coronary angioplasty. The Doppler velocity and hemodynamic signals were displayed and recorded on a photographic multichannel oscillographic recorder (Electronics for Medicine, VR12). Mean and phasic Doppler velocity signals were calibrated before catheter placement from an internally set arbitrary calibration of 0 to

100 cm/s, representing full scale deflection. In all patients, attempts were made to avoid large side branches (>12% diameter of major vessel) and eccentric catheter locations (causing unsuitable phasic signals).

After stable, satisfactory mean and phasic velocity signals were obtained, 10 mg of papaverine in 10 cc of normal saline solution was injected as a bolus over 3 s into the left coronary artery during continuous recording of hemodynamic variables, coronary artery flow velocity and echocardiographic left ventricular wall motion through peak hyperemia and for 120 s of recovery. Seven patients received 200 μg of intracoronary nitroglycerin before administration of papaverine, with a 3 min equilibration and return to baseline before papaverine. After a 3 min equilibration period, a duplicate set of baseline and hemodynamic measurements was again obtained for the second intracoronary injection of 10 to 12 mg of papaverine. This injection was used to assess reproducibility and to verify the maximal vasodilator effect of papaverine (7).

**Coronary angioplasty technique.** After the precoronary angioplasty data were obtained, the Doppler catheter was then exchanged for an appropriately sized coronary angioplasty balloon catheter (2.0 to 3.5 mm diameter) over the guide wire for coronary dilation. Translesional aortocoronary pressure gradients were measured when feasible (n = 10 before dilation, n = 12 final). Coronary balloon inflations (usually three to five at 6 to 10 atm for 60 to 120s) were performed. After satisfactory angiographic and hemodynamic coronary angioplasty results were obtained, the coronary angioplasty catheter was again exchanged for the Doppler catheter and papaverine hyperemia-echocardiographic data were collected 30 to 45 min later in the identical manner as before coronary angioplasty.

**Intravenous dipyridamole methodology.** In the 13 group 2 patients with prior angiographic demonstration of single vessel coronary disease, two-dimensional echocardiographic left ventricular wall motion data were obtained at baseline and at peak hyperermic dipyridamole effect. Dipyridamole was infused intravenously at a rate of 0.14 mg/kg per min over 4 min, for a total dose of 0.56 mg/kg after a baseline echocardiographic study. Three minutes of isometric handgrip exercise was then performed (9), and repeat two-dimensional echocardiographic examination of left ventricular wall motion was obtained. Two-dimensional parasternal short-axis images were recorded at the level of the mitral valve leaflets and the papillary muscles before the administration of intravenous dipyridamole. Apical two and four chamber images were recorded from the cardiac apex. For both papaverine and dipyridamole, the chest was marked for optimal transducer location for repositioning after intervention.

**Angiographic data analysis.** Angiographic assessment of coronary stenosis for groups 1 and 2 was performed by computer-assisted caliper measurements from the projected 35 mm coronary cineangiographic films on a General Electric Cap 12 projector. The diameters of the normal segments of the artery and the pre- and postcoronary angioplasty stenosis diameters were obtained, with the absolute values computed with use of the known diameter of the guiding catheter as a calibrated reference. The percent diameter stenosis in both right and left anterior oblique views was averaged (when orthogonal views were available). The cross-sectional area computation of the normal portion of the vessel and minimal cross-sectional area of the stenosis assumed a circular geometry (cross-sectional area = $\pi (d/2)^2$, where d = diameter of stenosis in millimeters). It was also assumed that the rest diameter of the vessel was minimally affected by contrast medium or vasodilators at the time of velocity measurement. Overestimation of vasodilator reserve of approximately 16% with papaverine-induced vessel diameter enlargement has been reported (10). The length of the lesion was <0.5 cm in 12 patients undergoing coronary angioplasty.

**Coronary vasodilator reserve ratios.** These ratios were computed as the mean peak hyperemic flow/mean basal mean flow velocity. Absolute mean and peak phasic coronary artery velocity responses, as well as diastolic flow velocity integral (area from aortic dicrotic notch to systolic upstroke (Fig. 1), total diastolic time ($T_E$), time to peak velocity ($T_{pk}$), mean velocity acceleration (mACC) and first one-third ($I_{1/3}$) and first one-half ($I_{1/2}$) of diastolic flow velocity integrals were also assessed. A percent increase from baseline value was also computed as ([peak-basal]/basal value) × 100.

*Duplicate coronary responses to normal saline solution and papaverine* demonstrated reproducibility of arterial flow velocity values over the measurement periods within ±10%.

**Statistical method.** Each patient served as his or her own control. Data were analyzed by one-way analysis of variance for repeated measures. Stepwise linear regression was used for correlation coefficients for coronary reserve ratios with angiographic data. In addition, when analysis of variance was significant, comparisons of the mean values were made with use of Duncan's multiple range F statistic (11) and, where appropriate, paired and nonpaired Students *t* tests were performed. Chi-square test for discrete wall motion responses was applied. Statistically significant probability (p) values were accepted at $p < 0.05$. Results are expressed as mean values ± SD unless otherwise indicated.

## Results

**Clinical data (Table 1).** The patient groups were similar with respect to age and gender distribution. Left ventricular wall motion abnormalities at rest were present in similar proportions in both the papaverine (group 1) and dipyridamole (group 2) groups. No patient in group 1 and three patients in group 2 (Cases 3, 10 and 11) had inferior pathologic Q waves on the rest electrocardiogram. Patient 1 in

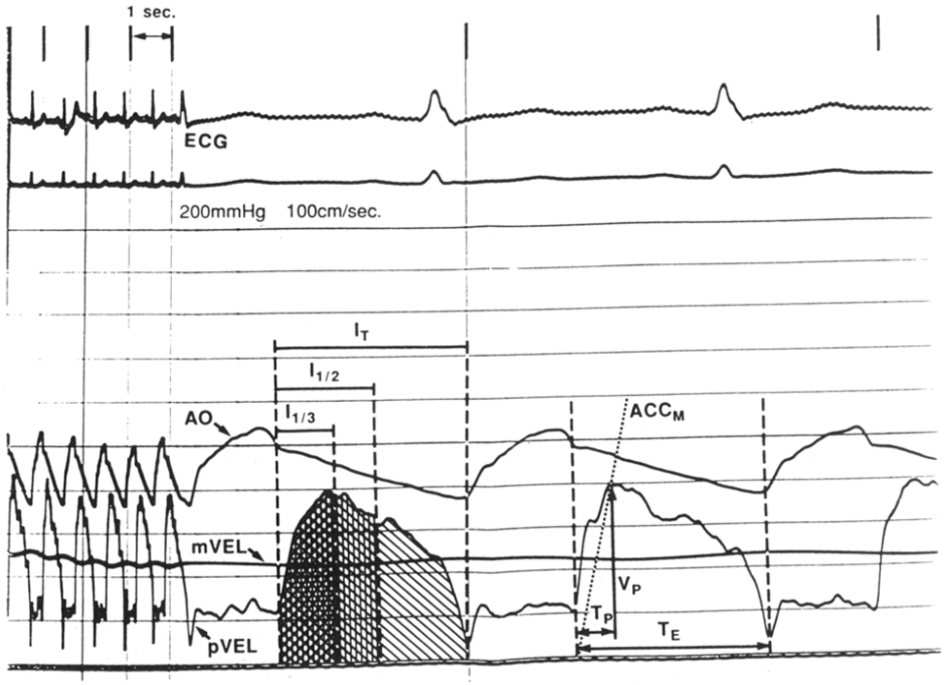


**Figure 1.** Intracoronary Doppler velocity signal. The diastolic flow integral area used to estimate volumetric flow is represented by the area $I_T$ bounded by the aortic (AO) dicrotic notch to the systolic upstroke. $ACC_M$ = mean velocity acceleration; ECG = electrocardiogram; $I_{1/2}$ = half diastolic flow velocity integral; mVEL = mean velocity signal (scale 0 to 100 cm/s); pVEL = phasic velocity signal; $T_E$ = total diastolic time; $T_p$ = time to peak velocity; $V_p$ = peak phasic velocity.

group 1 had left bundle branch block. Nonspecific anterior or anterolateral ST changes were present in three patients in group 1 and in one patient in group 2.

**Hemodynamic response to vasodilation (Table 2).** Rest and peak hemodynamic effects of both papaverine (group 1) and dipyridamole (group 2) were similar, with systolic, diastolic and mean arterial pressure decreasing −5 ± 8%, −4 ± 5% and −4 ± 6% for group 1, the normal group and group 2, respectively. The heart rate increased 7 ± 9%, 10 ± 10% and 11 ± 7%, respectively, with heart rate-blood pressure product increasing somewhat more for the dipyridamole group (14 ± 11% versus 3 ± 14% and 6 ± 4% for group 1 and the normal group, respectively, p = NS).

**Left ventricular wall motion abnormalities during coronary hyperemia (Table 3).** Table 3 shows baseline and peak papaverine or dipyridamole hyperemic left ventricular echocardiographic ventricular wall motion. Data for wall motion analysis after coronary angioplasty were unavailable for the dipyridamole group (group 2). Five of the group 1 (papaverine) patients (Cases 6, 7, 9, 11 and 12) demonstrated new left ventricular wall motion abnormalities during papaverine. Increased or hyperkinetic left ventricular wall motion was observed in Patients 1, 2, 5 and 14 during papaverine. After coronary angioplasty, improvement in wall motion was noted in Patients 7 and 9.

For dipyridamole-induced hyperemia (group 2), new left ventricular wall motion abnormalities were present in Patients 4, 7 and 8. No patient demonstrated improvement in wall motion.

**Angiographic data.** The percent left anterior descending stenosis was similar in the patients in group 1 (papaverine) and group 2 (dipyridamole) with single vessel coronary artery disease (74 ± 10% and 74 ± 14% before coronary angioplasty for groups 1 and 2, respectively) (Table 1); after coronary angioplasty was performed, stenosis diameter improved by 23 ± 22% and 27 ± 12%, respectively (Table 1). Aortocoronary pressure gradients, available in 13 of the 14 group 1 patients showed significant improvement (<30 mm Hg) in 10 patients after coronary angioplasty. Comparable quantitative angiographic data were present in group 1 and group 2 patients (11 of 13 angiograms in group 2 were available for analysis) (Table 4).

**Intracoronary velocity data (Table 4).** Coronary vascular reserve before and after coronary angioplasty in group 1 (papaverine) indicated a nonsignificant trend toward improvement in coronary reserve ratio. One patient (Case 14) had a coronary vascular reserve ratio >3.5 before coronary angioplasty and three patients (Cases 3, 4 and 14) had a coronary vascular reserve ratio >3.5 after coronary angioplasty (Table 4). No patient in group 1 with new regional asynergy had a coronary vascular reserve ratio >2.23 before coronary angioplasty and two patients with improved left ventricular wall motion after angioplasty had a coronary vascular reserve <1.75. Patient 13 (Table 4) had reocclusion after angioplasty of the left anterior descending coronary artery and underwent successful coronary bypass surgery; no postcoronary angioplasty data were obtained in this patient.

There were no significant differences with respect to absolute rest, peak phasic or mean flow velocity, mean acceleration time, total diastolic flow velocity integral, first third or first half velocity integrals between the normal group and the patients undergoing coronary angioplasty (group 1

**Table 1.** Clinical and Angiographic Data in 42 Patients

| Patient No. | Age (yr) & Gender | LVEF (%) | LVWM | % Stenosis*† | | Aortocoronary Gradient (mm Hg)† | |
|---|---|---|---|---|---|---|---|
| | | | | Pre | Post | Pre | Post |
| Group 1 (intracoronary papaverine) | | | | | | | |
| 1 | 59F | 43 | AH | 79 | 16 | 48 | 18 |
| 2 | 65F | 47 | IA | 79 | 24 | 40 | 20 |
| 3 | 36M | 60 | NL | 82 | 17 | 60 | 30 |
| 4 | 40M | 67 | NL | 73 | 8 | 45 | 20 |
| 5 | 40F | 59 | AH | 57 | 21 | 50 | 20 |
| 6 | 45F | 62 | NL | 73 | 20 | 65 | 38 |
| 7 | 40M | 85 | IH | 90 | 26 | — | 10 |
| 8 | 59M | 73 | NL | 77 | 26 | 50 | 28 |
| 9 | 63M | 73 | NL | 74(C) | 6 | 60 | 35 |
| 10 | 49M | 80 | NL | 58 | 10 | 45 | 10 |
| 11 | 57M | 62 | IA | 58(C) | 8 | 25 | 0 |
| 12 | 54M | — | NL | 82(C) | 19 | — | 0 |
| 13 | 66F | — | AH | 84 | 100 | 60 | — |
| 14 | 79F | 75 | NL | 67 | 16 | 40 | 35 |
| Mean ± SD | 54 ± 12 | 66 ± 12 | | 74 ± 10 | 23 ± 22 | 49 ± 11 | 20 ± 12 |
| Group 2 (intravenous dipyridamole) | | | | | | | |
| 1 | 57F | 51§ | NL | 95 | 50 | | |
| 2 | 58F | 54§ | NL | 62 | 23 | | |
| 3 | 41M | 63§ | NL | 80 | 25 | | |
| 4 | 66M | 56 | IH | 70 | 25 | | |
| 5 | 71M | 78 | NL | 80 | 10 | | |
| 6 | 63M | 54§ | NL | 95 | 30 | | |
| 7 | 44M | 74 | NL | 65 | 23 | | |
| 8 | 75M | 73 | NL | 99(R) | 23 | | |
| 9 | 63M | 68 | NL | 60 | 20 | | |
| 10 | 70M | 59 | NL | 95 | 50 | | |
| 11 | 62F | 45§ | AH | 75 | 20 | | |
| 12 | 46F | 51 | NL | 70 | — | | |
| 13 | 68F | 46§ | IH | 60(R) | — | | |
| Mean ± SD | 60 ± 10 | 59 ± 11 | | 77 ± 14 | 27 ± 12 | | |
| Normal group (intracoronary papaverine) | | | | | | | |
| 1 | 39M | 59 | NL | 0 | | | |
| 2‡ | 48M | 63 | AH | 40 | | | |
| 3 | 67M | 66 | NL | 0 | | | |
| 4 | 49M | 60 | NL | 0 | | | |
| 5‡ | 69M | 68 | NL | 0 | | | |
| Mean ± SD | 54 ± 12 | 63 ± 3 | | | | | |

*Percent stenosis of left anterior descending artery unless indicated as right (R) or circumflex (C) coronary artery. †Pre and Post refer to before and after coronary angioplasty. ‡Velocity data obtained in both left anterior descending and circumflex arteries. AH = anterior hypokinesia; F = female; IA = inferior akinesia; IH = inferior hypokinesia; LVEF = left ventricular ejection fraction (§echocardiographic); M = male; NL = normal; LVWM = left ventricular wall motion.

and normal subjects) (Table 2). As in previous studies (12), the coronary vasodilator reserve ratio was impaired relative to normal for the coronary angioplasty group both before (2.14 ± 1.05) (group 1) and after (group 1) coronary dilation (for the normal group, coronary vascular reserve = 3.22 ± 0.94, postcoronary angioplasty coronary reserve in group 1 = 2.43 ± 0.98, $p < 0.05$). The percent change in coronary velocity (both peak phasic and mean flow velocity) before coronary angioplasty, however, was significantly higher for normal arteries.

## Discussion

The results of this study indicate that neither intracoronary papaverine nor intravenous dipyridamole consistently elicited new echocardiographically determined left ventricular regional wall motion abnormalities in patients with a critical single vessel coronary artery narrowing without collateral supply. Regional asynergy may be elicited by pharmacologic stimuli in some patients with single vessel disease (1), but the reported subgroup of patients with a

**Table 2.** Hemodynamic and Intracoronary Velocity Data During Coronary Vasodilation

| | Before PTCA | | After PTCA | | | |
|---|---|---|---|---|---|---|
| | CON | PAP/DIP | CON | PAP | Before (% Δ) | After (% Δ) |
| SYS | | | | | | |
| PTCA | 121 ± 22 | 115 ± 18 | 123 ± 27 | 119 ± 24 | −4 ± 9 | −3 ± 12 |
| NL | 125 ± 21 | 121 ± 24 | — | — | −4 ± 6 | — |
| DIP | 130 ± 18 | 126 ± 19 | — | — | −3 ± 6 | — |
| DIA | | | | | | |
| PTCA | 68 ± 7 | 65 ± 9 | 71 ± 11 | 68 ± 11 | −4 ± 8 | −3 ± 9 |
| NL | 72 ± 8 | 69 ± 9 | — | — | −5 ± 4 | — |
| DIP | 79 ± 11 | 75 ± 7 | — | — | −4 ± 8 | — |
| MAP | | | | | | |
| PTCA | 87 ± 10 | 82 ± 9 | 88 ± 15 | 86 ± 14 | −5 ± 8 | −3 ± 10 |
| NL | 90 ± 12 | 86 ± 14 | — | — | −4 ± 5 | — |
| DIP | 96 ± 10 | 92 ± 9 | — | — | −4 ± 6 | — |
| HR | | | | | | |
| PTCA | 73 ± 14 | 79 ± 15 | 71 ± 12 | 75 ± 13 | 7 ± 9 | 6 ± 8 |
| NL | 65 ± 2 | 72 ± 8 | — | — | 10 ± 10 | — |
| DIP | 67 ± 13 | 78 ± 12 | — | — | 11 ± 7 | — |
| HR·SYS | | | | | | |
| PTCA | 8,857 ± 2197 | 9,050 ± 2267 | 8,800 ± 3,061 | 8,960 ± 2848 | 3 ± 14 | 4 ± 17 |
| NL | 8,207 ± 1438 | 8,644 ± 1326 | — | — | 6 ± 4 | — |
| DIP | 8,705 ± 2384 | 9,793 ± 2151 | — | — | 14 ± 11 | — |
| Phasic VEL | | | | | | |
| PTCA | 20 ± 9 | 38 ± 18 | 28 ± 15 | 48 ± 13 | 102 ± 93 | 112 ± 98 |
| NL | 16 ± 8 | 43 ± 12 | — | — | 204 ± 104* | — |
| Mean VEL | | | | | | |
| PTCA | 14 ± 7 | 27 ± 14 | 19 ± 10 | 36 ± 10 | 115 ± 119 | 119 ± 85 |
| NL | 10 ± 4 | 30 ± 10 | — | — | 222 ± 94* | — |
| RCV | | | | | | |
| PTCA | — | 0.52 ± 0.24 | — | 0.52 ± 0.21 | — | — |
| NL | — | 0.35 ± 0.016 | — | — | — | — |
| CVR | | | | | | |
| PTCA | — | 2.14 ± 1.05 | — | 2.43 ± 0.98 | — | — |
| NL | — | 3.22 ± 0.94* | — | — | — | — |

*$p < 0.05$ versus group I before/after angioplasty. CON = control; CVR = coronary vasodilatory reserve = (peak mean velocity [VEL]/basal mean velocity); DIA = diastolic pressure (mm Hg); DIP = dipyridamole (group 2); HR = heart rate (beats/min); HR·SYS = heart rate-systolic pressure product (mm Hg·beats·min$^{-1}$); MAP = mean arterial pressure (mm Hg); NL = normal group; phasic VEL = peak phasic velocity; PTCA = coronary angioplasty (group 1); RCV = ratio of coronary velocity normalized for mean arterial pressure (MAP) = (peak velocity/mean peak MAP)/basal velocity/mean basal MAP; SYS = systolic pressure (mm Hg); VEL = velocity; % Δ = ([papaverine-control]/control)·100.

positive response had a more severely occluded artery with a higher proportion of collaterally supplied vessels. Unlike prior studies suggesting that coronary reserve correlated with left ventricular functional response, our study indicated that the intracoronary velocity determination of coronary reserve did not identify those patients prone to having inducible new wall motion abnormalities. Anatomic and angiographic data with regard to size of the vessel, lesion diameter or cross-sectional area and improvement after coronary angioplasty did not further identify patients with hyperemic wall motion abnormalities. As a comparison with previously reported studies (1,13,14) of intravenous methods used in similar patients, analysis of dipyridamole-induced echocardiographic responses was attempted. Dipyridamole has similar effects on the augmentation of coronary blood flow (1,13) and velocity (14) as does papaverine.

**Mechanisms of pharmacologic-inducible regional asynergy.** In the presence of a critical coronary artery stenosis, increases in coronary blood flow by potent vasodilators such as papaverine, adenosine triphosphate, nitroglycerin and dipyridamole may cause a decrease in coronary perfusion pressure distal to the coronary stenosis (15,16). Thus, coronary vasodilators have the potential of producing subendocardial hypoperfusion secondary to a reduction in distal coronary perfusion, even though epicardial coronary blood flow is augmented. Alternatively, in patients with a critically narrowed vessel visualized by collateral flow, coronary vasodilators may produce regional asynergy by diverting or "stealing" blood from the collaterally supplied bed to a normal bed through dilation and reduction of distal coronary pressure in the normal coronary circuit (17).

*Picano et al. (1) demonstrated transient myocardial dys-*

**Table 3.** Echocardiographic Left Ventricular Wall Motion Responses to Pharmacologic Hyperemia in Groups 1 and 2

| | Before PTCA | | After PTCA | |
|---|---|---|---|---|
| Pt No. | Base | PAP | Base | PAP |
| Group 1 | | | | |
| 1 | A | H | A | H |
| 2 | A | H | A | H |
| 3 | N | N | N | N |
| 4 | N | N | N | N |
| 5 | A | H | A | H |
| 6 | N | H | H | H |
| 7 | N | H | N | N |
| 8 | N | N | N | N |
| 9 | H | D | H | A |
| 10 | N | N | N | N |
| 11 | N | H | N | H |
| 12 | N | H | N | H |
| 13 | N | N | — | — |
| 14 | N | U | N | N |
| | Base | DIP | Thallium | |
| Group 2 | | | | |
| 1 | N | N | N | |
| 2 | N | N | N | |
| 3 | N | N | R | |
| 4 | N | H | N | |
| 5 | N | N | R | |
| 6 | N | N | N | |
| 7 | N | LH | R | |
| 8 | N | LH | R | |
| 9 | N | N | N | |
| 10 | N | N | N | |
| 11 | H | H | F | |
| 12 | N | N | N | |
| 13 | IH | IH | F | |

A = akinesia; Base = baseline study; D = dyskinesia; F = fixed thallium defect; Group 1 = angioplasty (PTCA) group with intracoronary papaverine (PAP); Group 2 = group with intravenous dipyridamole (DIP); H = hypokinesia; I = inferior; L = lateral; N = normal; Pt = patient; R = redistribution thallium image; U = hyperkinesia.

*function during intravenous dipyridamole coronary vasodilation in 29 patients.* In 19 patients with an 80% to 99% proximal isolated left anterior descending artery stenosis, coronary hyperemia during dipyridamole infusion induced asynergy in 9 and no asynergy in 10. The coronary artery stenosis of similar angiographic severity produced different reductions in coronary reserve, as determined by analysis of great cardiac vein efflux. The impairment of myocardial contractility appeared to be related to patients with reduced coronary reserve (1).

*The findings of Picano et al. (1) were not duplicated in our study for at least four possible reasons:* 1) in none of the patients with single vessel disease in our study was angiographically or acutely recruited (distal coronary artery occlusion pressure >35 mm Hg) collateral supply to the distal vessel present; 2) selective hyperemia with papaverine, rather than global hyperemia with dipyridamole, may cause a different systemic hemodynamic/coronary, subepicardial/subendocardial flow distribution response; 3) the absolute cross-sectional area measurements in our study were computed from circular area ($0.51 \pm 0.42$ and $0.39 \pm 0.39$ mm$^2$ versus $0.34 \pm 0.12$ mm$^2$ of Picano et al. [1] with assumption of an eliptical geometry); and 4) the use of great cardiac vein efflux versus arterial velocity ratios of coronary reserve may provide different results. In the present analysis, left ventricular wall motion responses to both papaverine and dipyridamole in patients without collateral flow were of similar proportions. Differences in the heart rate-blood pressure product tended to be higher in the dipyridamole study group as a result of the addition of isometric stress to maximize coronary flow. Despite a potentially greater degree of myocardial demand and reduced coronary reserve, inducible left ventricular wall motion abnormalities were minimal.

*The current findings are consistent with an elegant study by Fung et al. (18),* who used two-dimensional echocardiography to examine left ventricular wall motion in an open chest animal model during intravenous dipyridamole-induced hyperemia in an artery with an artificial critical circumflex artery stenosis. They found that left ventricular wall motion abnormalities were produced in only 55% of the dogs. The low frequency of echocardiographic left ventricular wall motion abnormalities was attributed to inadequate production of "true" ischemia with preservation of regional subendocardial blood flow. We also postulate that the limited number of inducible wall motion abnormalities in our study is most likely due to maintenance of regional subendocardial blood flow in patients with a critical single vessel coronary narrowing and no collateral flow (either visible or acutely recruitable). The increased left ventricular wall motion observed in several patients after administration of papaverine may represent a reflex increase in contractility, albeit of small magnitude, in response to systemic vasodilation or tachycardia.

**Coronary vasodilator reserve and left ventricular function.** The mechanical behavior of the left ventricle in response to substantial coronary hyperemia through pharmacologic vasodilation reflects the cumulative hemodynamic severity of a stenosis more than the angiographic severity as assessed by percent luminal reduction, minimal cross-sectional area or coronary flow (or velocity) reserve in patients (1). The limitations of determining the physiologic importance of angiographic lesions are widely understood as a current unresolved methodologic dilemma in treating patients with coronary artery disease (19). To improve abnormal results related to severe coronary stenosis in our study, coronary angioplasty was performed and the measurements repeated. However, coronary flow velocity reserve after coronary angioplasty may not normalize in approximately 50% of patients (12), despite reports of improvement with thallium

**Table 4.** Angiographic and Coronary Reserve Data in Groups 1 and 2 Before and After Angioplasty

| Pt No. | Arterial Diameter (mm) | Stenosis Diameter (mm) | | Cross-Sectional Area (mm) | | Δ | %Δ | CVR | |
|---|---|---|---|---|---|---|---|---|---|
| | | Before | After | Before | After | | | Before | After |
| Group 1 | | | | | | | | | |
| 1 | 2.30 | 0.48 | 1.93 | 0.18 | 2.93 | 1.45 | 75.00 | 1.82 | 2.14 |
| 2 | 2.60 | 0.55 | 1.98 | 0.23 | 3.07 | 1.43 | 72.37 | 2.27 | 2.00 |
| 3 | 2.80 | 0.50 | 2.32 | 0.20 | 4.24 | 1.82 | 78.31 | 2.14 | 3.88 |
| 4 | 3.40 | 0.92 | 3.13 | 0.66 | 7.68 | 2.21 | 70.65 | 2.00 | 4.00 |
| 5 | 2.90 | 1.25 | 2.29 | 1.22 | 4.12 | 1.04 | 45.57 | 2.68 | 2.14 |
| 6 | 2.50 | 0.68 | 2.00 | 0.36 | 3.14 | 1.33 | 66.25 | 1.64(W) | 1.09 |
| 7 | 2.38 | 0.24 | 1.76 | 0.04 | 2.44 | 1.52 | 86.49 | 2.23(W) | 1.67(I) |
| 8 | 2.72 | 0.63 | 2.01 | 0.31 | 3.18 | 1.39 | 68.92 | 1.61 | 1.79 |
| 9 | 2.33 | 0.61 | 2.19 | 0.29 | 3.77 | 1.58 | 72.34 | 0.56(W) | 1.05(I) |
| 10 | 2.98 | 1.25 | 2.68 | 1.23 | 5.65 | 1.43 | 53.33 | 2.65 | 2.97 |
| 11 | 2.95 | 1.24 | 2.71 | 1.21 | 5.79 | 1.48 | 54.35 | 2.19(W) | 3.02 |
| 12 | 3.56 | 0.64 | 2.88 | 0.32 | 6.53 | 2.24 | 77.78 | 1.74(W) | 2.32 |
| 13 | 2.94 | 0.47 | — | 0.17 | — | — | — | 1.25 | — |
| 14 | 2.50 | 0.83 | 2.10 | 0.53 | 3.46 | 1.28 | 60.71 | 5.23 | 3.95 |
| Mean ± SD | 2.72 ± 0.31 | 0.74 ± 0.32 | 2.26 ± 0.38 | 0.51 ± 0.42 | 4.12 ± 1.46 | 1.50 ± 0.28 | 67.02 ± 11.15 | 2.14 ± 1.05 | 2.43 ± 0.98 |
| Group 2 | | | | | | | | | |
| 1 | 2.80 | 0.14 | 1.40 | 0.02 | 1.54 | 1.26 | 90.00 | | |
| 2 | 2.60 | 0.99 | 2.00 | 0.77 | 3.15 | 1.01 | 50.65 | | |
| 3 | 3.20 | 0.64 | 2.40 | 0.32 | 4.52 | 1.76 | 73.33 | | |
| 4 | 2.50 | 0.75 | 1.88 | 0.44 | 2.76 | 1.13 | 60.00(W) | | |
| 5 | 2.70 | 0.54 | 2.43 | 0.23 | 4.64 | 1.89 | 77.78 | | |
| 6 | 2.70 | 0.14 | 1.89 | 0.01 | 2.81 | 1.76 | 92.86 | | |
| 7 | 3.00 | 1.05 | 2.31 | 0.87 | 4.19 | 1.26 | 54.55(W) | | |
| 8 | 3.60 | 0.04 | 2.77 | .00 | 6.04 | 2.74 | 98.70(W) | | |
| 9 | 3.10 | 1.24 | 2.48 | 1.21 | 4.83 | 1.24 | 50.00 | | |
| 10 | 2.80 | 0.14 | 1.40 | 0.02 | 1.54 | 1.26 | 90.00 | | |
| 11 | 2.90 | 0.73 | 2.32 | 0.41 | 4.23 | 1.60 | 68.75 | | |
| 12 | — | — | — | — | — | — | — | | |
| 13 | — | — | — | — | — | — | — | | |
| Mean ± SD | 2.90 ± 0.30 | 0.58 ± 0.40 | 2.12 ± 0.42 | 0.39 ± 0.39 | 3.66 ± 1.35 | 1.54 ± 0.47 | 73.33 ± 17.08 | | |

CVR = coronary vasodilatory reserve (see text); I = improved left ventricular wall motion after angioplasty; Pt = patient; W = new left ventricular wall motion abnormality; Δ = change in diameter (mm) and % change in diameter (mm) before and after angioplasty; — = data not available.

perfusion (20) and radiographically determined flow reserve (21,22). Left ventricular wall motion improved in only two patients after reduction of epicardial luminal obstruction. Factors related to abnormal coronary reserve after coronary angioplasty include alteration of autoregulatory homeostasis involving the diseased small precapillary regulatory arterioles (23,24), vascular smooth muscle damage (25,26), endothelial vasomotor factor release or inhibition (27–31), local release of circulating factors directly affecting coronary vasomotor tone (30) or activation and release of platelet-mediated vasomotor products (28,29).

In only one patient was the coronary vascular reserve value before coronary angioplasty above previously published (12,32) lower range normal limits (>3.5 units). After coronary angioplasty, coronary vascular reserve improved to above or near normal ranges in only three patients. No correlation with coronary reserve improvement and papaverine-induced left ventricular wall motion abnormalities after coronary angioplasty was observed. The impaired coronary flow vasodilator reserve responses observed in this and other studies (12,31) most likely reflect the multiple mechanisms discussed and others yet to be defined. Nonetheless, failure to improve abnormal left ventricular wall motion initially after coronary angioplasty is consistent with residual attenuated coronary reserve after coronary angioplasty. In the two patients showing immediate wall motion improvement, coronary reserve did not appear to change in a consistent manner.

**Coronary flow responses to papaverine and dipyridamole.** Studies of regional coronary blood flow have not directly compared intracoronary papaverine and intravenous dipyridamole in the same patients. Intracoronary papaverine (10 mg) increased coronary sinus (13) or coronary artery (14) flow velocity in patients with normal vessels and those with single vessel left anterior descending coronary artery stenosis (400 ± 100 and 75 ± 40%, respectively) (14,33). Intrave-

nous dipyridamole increased coronary flow 400 ± 240% and 45 ± 30%, for normal subjects and patients with coronary artery disease, respectively (12–14). Intracoronary dipyridamole increased coronary sinus flow 73% compared with an increase of 172% after intravenous dipyridamole in the same patients (13). The difference in coronary flow responses between routes of administration is attributed to increased myocardial oxygen demand with systemic effects (increased heart rate, cardiac output and pulmonary artery pressures) of dipyridamole.

**Limitations.** Several limitations of clinical studies of this type deserve comment. These results may reflect the previously acknowledged low sensitivity of two-dimensional echocardiographic assessment of left ventricular wall motion after coronary vasodilators for patients with varying degrees of coronary artery disease. The sensitivity increases proportionately with disease involvement, with studies (2,3,34–37) reporting sensitivity (individual study values averaged) for single, double and triple vessel coronary artery disease of 37, 71 and 100%, respectively.

*Artifacts and limitations of echocardiographic left ventricular wall motion analysis* are well known and have been described in detail elsewhere (1–3). The few differences in angiographic (Table 1) and echocardiographic left ventricular wall motion measurements used to identify inducible regional asynergy can be attributed to differences in techniques. Two-dimensional echocardiographic views used during the study were selected to visualize regions of interest, and wall motion in remote areas were not included.

*Although angiographic computations of cross-sectional area in this study are only approximate* because quantitative digital radiographic techniques (38) were not yet available in our laboratory, coronary lumen dimensions were significantly reduced in all patients with coronary artery disease, with markedly reduced coronary vascular reserve in 13 of the 14 (group 1) patients undergoing coronary angioplasty. Suboptimal or subselective intracoronary vasodilatory drug administration may result in different concentrations being delivered to the target vessel. Attention was given to identical catheter positioning for drug delivery. We attempted to duplicate catheter position proximal to the coronary angioplasty site and use of signals with clearly demarcated phasic wave forms for analysis.

*Another possible explanation for the limited number of inducible left ventricular wall motion abnormalities* would be an insufficient hyperemic stimulus with papaverine. The transient hyperemia may not provide sufficient duration or magnitude of oxygen debt to elicit contraction abnormalities. However, global hyperemia as predicted to occur with dipyridamole resulted in a similar low incidence of regional asynergy in a nearly identical group of patients.

**Conclusion.** Although two-dimensional echocardiography appears to be useful in identifying patients with multivessel coronary artery disease (1–3), the immediate evaluation in the catheterization laboratory of left ventricular regional asynergy induced by selective pharmacologic coronary hyperemia does not appear to be an adequate indicator of angiographically severe single vessel coronary stenosis.

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## References

1. Picano E, Simonetti I, Masini M, et al. Transient myocardial dysfunction during pharmacologic vasodilation as an index of reduced coronary reserve: a coronary hemodynamic and echocardiographic study. J Am Coll Cardiol 1986;8:84–90.
2. Picano E, Distante A, Masini M, Morales MA, Lattanzi F, L'Abbate A. Dipyridamole echocardiography test in effort angina pectoris. Am J Cardiol 1985;56:452–6.
3. Labovitz AJ, Pearson AC, Chaitman BR. Doppler and two-dimensional echocardiographic assessment of LV function before and after intravenous dipyridamole stress testing for detection of coronary artery disease. Am J Cardiol 1988;62:1180–5.
4. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of the coronary stenosis? N Engl J Med 1984;310:819–24.
5. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Am J Cardiol 1974;33:87–94.
6. Gould KL. Noninvasive assessment of coronary stenosis by myocardial perfusion imaging during pharmacologic coronary vasodilatation. I. Physiologic basis and experimental validation. Am J Cardiol 1978;41:267–76.
7. Wilson RF, Laughlin DE, Ackell PH, et al. Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. Circulation 1985;1:82–92.
8. Sibley DH, Millar HD, Hartley CJ, Whitlow PL. Subselective measurement of coronary blood flow velocity using a steerable Doppler catheter. J Am Coll Cardiol 1986;8:1332–40.
9. Brown BG, Josephson MA, Petersen RB, et al. Intravenous dipyridamole combined with isometric handgrip for near maximal acute increase in coronary flow in patients with coronary artery disease. Am J Cardiol 1981;48:1077–85.
10. Zijlstra F, Reiber JHC, Serruys PW. Does intracoronary papaverine dilate epicardial coronary arteries: implications for the assessment of coronary flow reserve. Cathet Cardiovasc Diagn 1988;114:1–6.
11. Duncan DB. Multiple range and multiple F tests. Biometrics 1955;11:1–2.
12. Wilson RF, Johnson MR, Marcus ML, et al. The effect of coronary angioplasty on coronary flow reserve. Circulation 1988;77:873–85.
13. Marchant E, Pichard A, Rodriguez JA, Casanegra P. Acute effect of systemic versus intracoronary dipyridamole on coronary circulation. Am J Cardiol 1986;57:1401–4.
14. Wilson RF, White CW. Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in conscious humans. Circulation 1986;73:444–51.
16. Hintze TH, Vatner SF. Reactive dilation of large coronary arteries in conscious dogs. Circ Res 1984;54:50–7.
17. Fam WM, McGregor M. Effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. Circ Res 1964;15:355–65.
18. Fung AY, Gallagher KP, Buda AJ. The physiologic basis of dobutamine as compared with dipyridamole stress interventions in the assessment of critical coronary stenosis. Circulation 1987;76:943–51.

19. Klocke FJ. Measurements of coronary flow reserve: defining pathophysiology versus making decisions about patient care. Circulation 1987;76:1183–9.

20. Wahr DW, Ports TA, Botvinick EH, et al. The effects of coronary angioplasty and reperfusion on distribution of myocardial flow. Circulation 1985;72:334–43.

21. Hodgson JM, Riley RS, Most AS, Williams DO. Assessment of coronary flow reserve using digital angiography before and after successful percutaneous transluminal coronary angioplasty. Am J Cardiol 1987;60:61–5.

22. Zijlstra F, Reiber JC, Juilliere Y, Serruys PW. Normalization of coronary flow reserve by percutaneous transluminal coronary angioplasty. Am J Cardiol 1988;61:55–60.

23. Macho P, Hintze TH, Vatner SF. Regulation of large coronary arteries by increases in myocardial metabolic demand in the conscious dog. Circ Res 1981;49:594–9.

24. Olsson RA. Myocardial reactive hyperemia. Circulation 1975;37:263–70.

25. Soward AL, Essed CE, Serruys PW. Coronary arterial findings after accidental death immediately after successful percutaneous transluminal coronary angioplasty. Am J Cardiol 1985;45:794–5.

26. Waller BF. Early and late morphologic changes in human coronary arteries after percutaneous transluminal coronary angioplasty. Clin Cardiol 1983;6:363–72.

27. Ludmer PL, Selwyn AP, Shook TL, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046–51.

28. Holtz J, Forstermann U, Pohl U, Giesler M, Bassenge E. Flow dependent endothelial mediated dilation of epicardial arteries in the conscious dog: effects of cycloxygenase inhibition. J Cardiovasc Pharmacol 1984;6:1161–9.

29. Inoue T, Tomoike H, Hisano K, Nakamura M. Endothelium determines flow-dependent dilation of the epicardial coronary artery in dogs. J Am Coll Cardiol 1988;11:187–95.

30. Yokoyama M, Akita H, Mizutani T, Fukazaki H, Watanabe Y. Hyperreactivity of coronary arterial smooth muscle in response to ergonovine from rabbits with hereditary hyperlipidemia. Circ Res 1983;53:63–71.

31. Wilson RF, White CW. Does coronary artery bypass surgery restore normal maximal coronary flow reserve? Circulation 1987;76:563–71.

32. Wilson RF, Marcus ML, White CW. Prediction of the physiologic significance of coronary arterial lesions by quantitative lesion geometry in patients with limited coronary artery disease. Circulation 1987;75:723–32.

33. Zijlstra F, Serruys PW, Hugenholtz PG. The ideal coronary vasodilator for investigating coronary flow reserve? A study of timing, magnitude, reproducibility, and safety of the coronary hyperemic response after intracoronary papaverine. Cathet Cardiovasc Diagn 1986;12:298–303.

34. Margonato A, Chierchia S, Cianflone E, et al. Limitations of dipyridamole-echocardiography in effort angina pectoris. Am J Cardiol 1987;59:225–30.

35. Picano E, Morales MA, Distante A, et al. Dipyridamole-echocardiography test in angina at rest: noninvasive assessment of coronary stenosis underlying spasm. Am Heart J 1986;111:688–91.

36. Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. Comparison of the high-dose dipyridamole-echocardiography test and exercise two-dimensional echocardiography for diagnosis for coronary artery disease. Am J Cardiol 1987;59:539–42.

37. Distante A, Picano E, Moscarelli E, Palombo C, Benassi A, L'Abbate A. Echocardiographic versus hemodynamic monitoring during attacks of variant angina pectoris. Am J Cardiol 1985;55:1319–22.

38. Rosenberg MC, Klein LW, Agarwal JB, Stets G, Hermann GA, Helfant RH. Quantification of absolute luminal diameter by computer-analyzed digital subtraction angiography: an assessment in human coronary arteries. Circulation 1988;77:484–90.