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## Relation between graded, subcritical impairments of coronary flow reserve and regional myocardial dysfunction induced by isoproterenol infusion in dogs

Isoproterenol has been used experimentally and clinically to elicit ischemia. The usefulness of this approach, however, in eliciting regional dysfunction in the presence of mild to moderate single-vessel coronary disease quantitated on the basis of coronary flow reserve measurements has not been previously defined. Open-chest, anesthetized dogs were instrumented with an electromagnetic flow probe, high-fidelity micromanometers, and subendocardial ultrasonic crystals. A rigid, screw occluder was used to produce five subcritical coronary stenoses in each dog associated with varying impairment of postocclusion reactive hyperemia at rest but no impairment of resting coronary blood flow. Regional function at rest and in response to the isoproterenol challenge (0.25  $\mu\text{g}/\text{kg}/\text{min}$ ) in nonstenotic and stenotic conditions was assessed. Relative regional function was maintained during the infusion until nearly total loss of coronary flow reserve. With this near-critical stenosis, function was lower than in the nonstenotic state but remained greater than resting control values. Moderate impairments of coronary flow reserve were not associated with isoproterenol-induced deterioration of regional function. In conclusion, detection of impaired coronary flow reserve at rest is a more sensitive index of the severity of a coronary stenosis than is detection of regional dysfunction during isoproterenol challenge. Failure to maintain the expected isoproterenol-induced increase in regional function is manifested only when stenoses are associated with nearly total loss of resting coronary flow reserve. This suggests that the clinical use of isoproterenol challenge is not effective in eliciting regional dysfunction when mild coronary disease is present. (*Am Heart J* 1987;113:906.)

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**Table 1.** Hemodynamics at rest and during isoproterenol infusions in the presence and absence of coronary stenoses: Part A

	Control	Isoproterenol infusion (0.25 µg/kg/min)			
		No stenosis	Stenosis 1	Stenosis 2	Stenosis 3
Heart rate (bpm)	155 ± 7	202 ± 10*	195 ± 9*	201 ± 7*	197 ± 8*
Left ventricular end-diastolic pressure (mm Hg)	8 ± 1	5 ± 1	6 ± 1	7 ± 1	8 ± 1†
Systolic blood pressure (mm Hg)	133 ± 5	139 ± 7	135 ± 6	133 ± 6	132 ± 5
Mean aortic pressure (mm Hg)	115 ± 6	102 ± 5*	104 ± 5*	101 ± 5*	97 ± 5*
Peak positive dP/dt (mm Hg/sec)	2038 ± 178	3782 ± 234*	3794 ± 215*	3524 ± 189*	3244 ± 210*,‡
Peak negative dP/dt (mm Hg/sec)	1961 ± 108	2267 ± 123	2279 ± 87	2389 ± 164§	2142 ± 122

dP/dt = rate of change of pressure with time; values are mean ± SEM.

\**p* < 0.001 vs control; †*p* < 0.05 vs no stenosis; ‡*p* < 0.001 vs no stenosis; §*p* < 0.01 vs control.

Gould et al.<sup>1</sup> demonstrated that only very severe coronary stenoses cause an impairment of resting coronary blood flow, whereas less severe lesions, within an approximate range of 45% to 90% diameter stenosis, show a relatively linear impairment of reactive hyperemia. With more severe lesions, reactive hyperemia is abolished. This concept provides a convenient measure of the potential importance of moderately severe coronary lesions which do not impair resting blood flow or regional function. This range of severity of coronary lesions is perhaps most clinically relevant because patients develop angina during stress, presumably because of exhaustion of flow reserve secondary to lesions which, nevertheless, allow sufficient blood flow to prevent symptoms at rest. Thus, in the evaluation of patients with suspected coronary disease, tests which can detect abnormalities associated with lower grade obstructions are expected to be of greatest use.

Recently, direct measurement of coronary flow reserve<sup>2,3</sup> has been proposed as an alternative approach to the assessment of the importance of coronary lesions in humans. Many patients have a relative diminution or "subcritical" impairment of flow reserve in contrast to a total abolition of flow reserve. One would expect that lesions associated with these subcritical impairments of coronary flow reserve could be detected under conditions of stress. Traditional methods used to do this include the various forms of exercise stress testing and nonexercise methods to elicit regional heterogeneity of coronary perfusion, wall motion abnormalities, or ECG findings. Thus, while it is interesting to note that the relation between arteriographically defined stenoses and coronary flow reserve measurements in patients is imperfect,<sup>4</sup> the relation between detected impairments of coronary reserve and evocation of stress-induced abnormalities has not been extensively studied.<sup>5-8</sup> Such studies would be of relevance

in helping to define the utility of the flow reserve index compared to the more traditional exercise and nonexercise methods used by the clinician to assess the functional importance of a coronary lesion. This is underscored by the fact that methods are becoming available that may allow nearly routine measurement of this index in patients.<sup>3,9-12</sup>

Beta-adrenergic agonists improve myocardial contractility but, in the setting of coronary artery stenoses, this effect may also aggravate supply-demand imbalances.<sup>13,14</sup> As a consequence, these agents have been used both experimentally and clinically to unmask functionally significant coronary stenoses.<sup>13-27</sup> When isoproterenol has been used in this fashion, regional dysfunction has been shown experimentally only in the setting of very severe coronary stenoses.<sup>20</sup> The ability to elicit dysfunction in the face of subcritical stenoses, defined on the basis of reductions of flow reserve, has not been studied. As argued previously, tests which can detect abnormalities associated with lower grade obstructions would be of greatest use, thus emphasizing the importance of studying such methods with regard to subcritical coronary lesions. Therefore, the purpose of this experiment was to establish the effects of isoproterenol on regional function in the face of mild, single-vessel coronary stenoses defined on the basis of graded, subcritical impairments of coronary flow reserve.

#### METHODS

**Definitions.** The following definitions of terms will be used for this experiment. A "critical" coronary stenosis is one associated with a flow reserve ratio of one and a concomitant mild impairment of resting coronary blood flow. A "subcritical" coronary stenosis is one associated normal resting blood flow and a coronary flow reserve value of greater than one but less than the value measured in the absence of a stenosis. A "near-critical" stenosis is one with a flow reserve ratio of nearly one. Relative

**Table II.** Regional function parameters at rest and during isoproterenol infusions in the presence and absence of coronary stenoses: Part A

	<i>Isoproterenol infusion (0.25 µg/kg/min)</i>				
	<i>Control</i>	<i>No stenosis</i>	<i>Stenosis 1</i>	<i>Stenosis 2</i>	<i>Stenosis 3</i>
<b>Ischemic zone</b>					
End-diastolic segment length (mm)	9.9 ± 0.4	9.8 ± 0.5	9.7 ± 0.5	9.8 ± 0.5	10.4 ± 0.5
End-systolic segment length (mm)	8.0 ± 0.4	6.8 ± 0.5*	6.83 ± 0.5*	7.1 ± 0.5†	8.7 ± 0.6†
Fractional shortening (%)	19.7 ± 2.0	30.9 ± 3.2§	29.4 ± 3.2§	27.3 ± 3.1*	17.4 ± 3.3‡
Fractional shortening (% of control)	—	160 ± 11	152 ± 10	138 ± 9	74 ± 15‡
<b>Nonischemic zone</b>					
End-diastolic segment length (mm)	10.4 ± 0.8	9.7 ± 0.7*	9.7 ± 0.7*	9.8 ± 0.7*	10.3 ± 0.7
End-systolic segment length (mm)	9.1 ± 0.7	7.9 ± 0.5§	7.9 ± 0.5§	7.8 ± 0.4§	8.0 ± 0.4§
Fractional shortening (%)	12.7 ± 1.6	19.1 ± 1.3§	18.2 ± 1.9*	20.0 ± 2.3§	21.6 ± 2.1§
Fractional shortening (% of control)	—	185 ± 38	183 ± 57	202 ± 55	197 ± 38

Values are mean ± SEM.

\**p* < 0.01 vs control; †*p* < 0.05 vs control; ‡*p* < 0.001 vs no stenosis; §*p* < 0.001 vs control; ||*p* < 0.05 vs no stenosis.

coronary flow is flow divided by flow during a resting, control state in the absence of isoproterenol infusion.

**Animal preparation.** Twenty-three mongrel dogs of either sex (average weight 24.6 kg, range 22.7 to 35.7) were anesthetized with intravenous pentobarbital sodium (35 mg/kg) and ventilated with room air by means of a Harvard respirator. A left thoracotomy was performed in the fifth intercostal space. The left anterior descending or the circumflex coronary artery was dissected free for a length of 1 to 2 cm and instrumented with a snare occluder, a hard plastic screw occluder, or a rubber cuff occluder (R. E. Jones, Silver Spring, Md.) and an appropriately sized electromagnetic flow probe (Carolina Medical Electronics, Inc., King, North Carolina). All flow probes were calibrated by means of timed collections of blood of known hematocrit infused at physiologic blood flow rates. Two pairs of subendocardial ultrasonic quartz crystals were implanted in the midequatorial region of the left ventricle and approximately parallel to the circumferential plane. One pair was implanted in the left anterior descending coronary artery distribution distal to the occluder and in the central area of the zone rendered dyskinetic and cyanotic during coronary occlusion (ischemic zone), and one pair was implanted in the left circumflex coronary artery region (nonischemic zone). In four studies the circumflex bed was used as the ischemic zone. The crystals were connected to a Sonomicrometer 120 (Triton Technology, San Diego, Calif.). Proper crystal alignment was confirmed in three ways: by oscilloscopic display of the sonomicrometer signals (Tektronix, Inc., Beaverton, Ore., model 2213A) during the experiment, by ensuring that total coronary occlusion elicited prompt dyskinetic regional function, and by dissection and direct inspection of the crystal position after the study. All crystals were within the inner one third of the myocardial wall, but misalignment was noted in five experiments which were excluded from data analysis. A 5F high-fidelity micromanometer (Millar Instruments, Inc., Hous-

ton, Tex) was inserted through a stab wound into the apex of the left ventricle for measurement of left ventricular pressure and its first derivative (dP/dt). A second 5F high-fidelity micromanometer was passed into the ascending aorta through a carotid arteriotomy.

**Experimental protocol.** Heart rate, rate of left ventricular pressure change with time (dP/dt), left ventricular pressure, mean aortic pressure, subendocardial segment lengths for the left anterior descending and circumflex regions, and phasic and mean coronary blood flow were recorded continuously on a Gould 2800S recorder.

The experiment was undertaken in two parts. In part A the severity of the stenoses was characterized only by the relative changes in coronary blood flow induced during a 3- to 5-minute steady-state infusion of isoproterenol (0.25 µg/kg/min). Observations were made during the control state and during isoproterenol infusion in the absence of a stenosis. Three levels of coronary stenosis were achieved by progressive coronary occlusion with a rubber cuff occluder during the isoproterenol infusion. The goal was to study impairment of coronary blood flow with a mild stenosis (stenosis No. 1) that decreased blood flow to a level midway between resting and maximal flow seen during infusion in the absence of a stenosis, a more severe stenosis (stenosis No. 2) that limited flow to resting levels during the infusion, and a very severe stenosis (stenosis No. 3) that reduced blood flow to approximately one half of the resting flow. Complete recovery was allowed between tests of each stenosis so that hemodynamic segment length and coronary blood flow measurements had returned to control levels. The absolute level of coronary blood flow rose minimally above control levels in response to isoproterenol in some dogs, possibly because of a decrease in aortic perfusion pressure, and this precluded a full complement of observations at the desired relative blood flow levels described above. These dogs were excluded from data analysis leaving nine dogs with a full complement of observations.

**Table III.** Coronary flow parameters of the ischemic zone at rest and during isoproterenol infusion in the presence and absence of coronary stenoses: Part A

	Isoproterenol infusion (0.25 µg/kg/min)				
	Control	No stenosis	Stenosis 1	Stenosis 2	Stenosis 3
Coronary blood flow (ml/min)	36.1 ± 5.0	53.8 ± 7.6*	48.3 ± 6.6†	32.0 ± 4.8‡	16.8 ± 3.2*‡
Coronary blood flow (% control)	—	153 ± 12	136 ± 7	89 ± 4‡	49 ± 3‡

Values are mean ± SEM.

\* $p < 0.001$  vs control; † $p < 0.01$  vs control; ‡ $p < 0.001$  vs no stenosis.

In part B, the severity of the stenoses was quantitated by the impairment of resting coronary flow reserve. Coronary flow reserve was determined at rest in the absence of a stenosis by the ratio of peak blood flow after a 20-second total occlusion to resting coronary blood flow. Isoproterenol was then infused for 3 to 5 minutes in the absence of a stenosis. After full recovery, isoproterenol was again infused, and a rigid, plastic screw occluder was then tightened slightly. After 3 to 5 minutes of infusion, full recovery was allowed and coronary flow reserve at rest was reassessed before any alteration of the occluder was made. This sequence was repeated in random order to create five different stenoses that impaired coronary flow reserve but did not impair resting coronary blood flow. The stenoses created within each dog were reassigned on the basis of the degree of impairment of coronary flow reserve. The mildest impairment was considered stenosis No. 1 and the maximal impairment was considered stenosis No. 5. This allowed creation of five stenotic groups containing one observation from each dog with statistically significant differences in the degree of coronary flow reserve impairment (see below). It should be emphasized that collapse or expansion of the screw occluder could not occur between the resting and infusion phases of the protocol. In addition, stenoses that impaired resting coronary blood flow were excluded from analysis to constrain observations in the subcritical range. A full complement of observations was achieved in nine dogs.

**Data analysis.** End-diastolic segment lengths and left ventricular end-diastolic pressures were determined at the beginning of left ventricular contraction when the dP/dt became positive. End-systolic segment lengths were determined at peak negative dP/dt.<sup>28</sup> Percentage of systolic shortening was determined by calculating the ratio of end-diastolic segment length minus end-systolic segment length to end-diastolic segment length multiplied by 100. All measurements were obtained by averaging data from three to five normally conducted beats. These were made at rest and during isoproterenol infusion in the absence of a stenosis and for each new level of coronary stenosis.

The coronary flow reserve was expressed both as the simple ratio and as a percentage of the maximal coronary flow reserve obtained in the absence of a coronary stenosis. The percentage of maximal coronary flow reserve was determined by:  $(CFR - 1)/(CFR_{max} - 1) \times 100\%$ , where

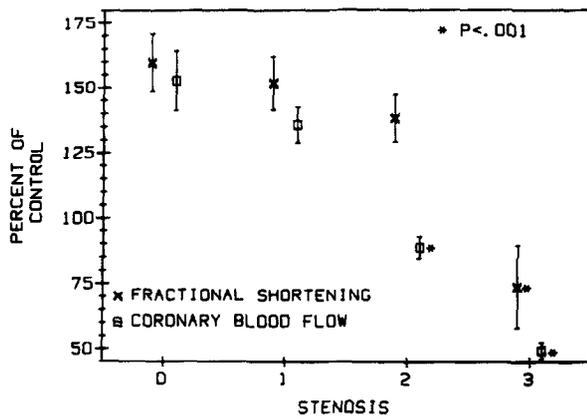
CFR = measured coronary flow reserve associated with any lesion and  $CFR_{max}$  = the maximal coronary flow reserve in the absence of a coronary stenosis.<sup>6,7</sup>

**Statistical analysis.** Data for all parameters were analyzed by means of repeated-measures analysis of variance. When overall significance was detected, a Bonferroni test was used to determine which stenosis stages differed from the resting control stage and/or the nonstenosis infusion stage.<sup>29</sup> Data analysis for part B also incorporated the use of paired *t* tests to determine if there was a significant difference between coronary blood flow at rest and during infusion for each stenosis level. Tukey's test was used to assess differences among reactive hyperemia values associated with each stenosis.<sup>29</sup> Correlations were performed by linear, logarithmic, and polynomial regression analysis. Data are reported as mean ± standard error of the mean (SEM). Findings were considered significant when  $p < 0.05$ .

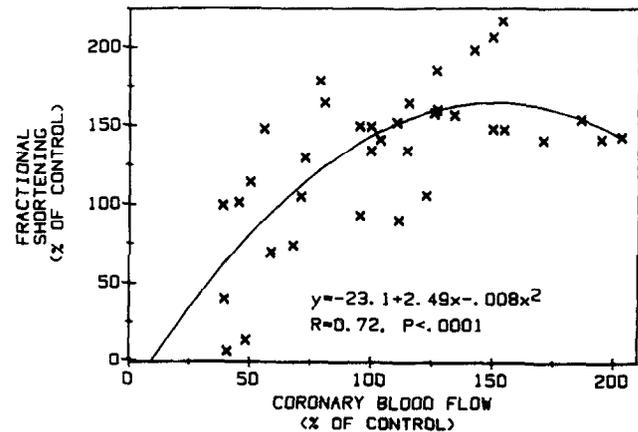
## RESULTS

**Part A.** Table I summarizes the hemodynamic effects of isoproterenol during the five stages of the protocol. The expected increases in heart rate and peak positive dP/dt and decrease in mean aortic pressure were noted during isoproterenol infusion. Table II summarizes the regional segment shortening data. The fractional shortening results showed an increase with isoproterenol from  $19.7 \pm 2.0\%$  to  $30.9 \pm 3.2\%$  ( $p < 0.001$ ) in the absence of a stenosis. Regional function fell progressively, but not significantly, to  $29.4 \pm 3.2\%$  and  $27.3 \pm 3.1\%$  for stenoses Nos. 1 and 2, respectively, and then to  $17.4 \pm 3.3\%$  for stenosis No. 3 ( $p < 0.001$  vs no stenosis).

The coronary blood flow (Table III) at rest was  $36.1 \pm 5.0$  cc/min and rose to  $53.8 \pm 7.6$  cc/min in the absence of a stenosis ( $p < 0.001$ ). With stenosis No. 1, coronary flow was greater than control values ( $48.3 \pm 6.6$  cc/min,  $p < 0.01$ ) but not significantly less than during isoproterenol infusion without a stenosis. With stenosis No. 2, flow was not different from control levels ( $32.0 \pm 4.8$  ml/min,  $p = NS$ ) but was decreased relative to the nonstenotic state ( $p < 0.001$ ). Coronary flow with the most severe



**Fig. 1.** Fractional shortening and coronary blood flow are shown for part A of the experimental protocol in the absence of stenosis and during three progressively severe stenoses. \* $p < 0.001$  vs nonstenotic control state. Values are mean  $\pm$  SEM;  $n = 9$ .



**Fig. 2.** Relation between coronary blood flow and fractional shortening is shown. Symbols represent individual observations from nine dogs in part A.

**Table IV.** Hemodynamics at rest and during isoproterenol infusions in the presence and absence of coronary stenoses: Part B

	Isoproterenol infusion (0.25 $\mu\text{g}/\text{kg}/\text{min}$ )						
	Control	No stenosis	Stenosis 1	Stenosis 2	Stenosis 3	Stenosis 4	Stenosis 5
Heart rate (bpm)	150 $\pm$ 8	192 $\pm$ 10*	187 $\pm$ 8*	187 $\pm$ 8*	187 $\pm$ 7*	191 $\pm$ 7*	191 $\pm$ 9*
Left ventricular end-diastolic pressure (mm Hg)	8 $\pm$ 1	6 $\pm$ 1†	6 $\pm$ 1	7 $\pm$ 1	7 $\pm$ 1	6 $\pm$ 1	7 $\pm$ 1
Systolic blood pressure (mm Hg)	133 $\pm$ 5	142 $\pm$ 6	136 $\pm$ 6	137 $\pm$ 5	138 $\pm$ 5	138 $\pm$ 6	136 $\pm$ 4
Mean aortic pressure (mm Hg)	115 $\pm$ 6	103 $\pm$ 5†	102 $\pm$ 4*	101 $\pm$ 3*	103 $\pm$ 4†	106 $\pm$ 5	103 $\pm$ 5†
Peak positive dP/dt (mm Hg/sec)	2042 $\pm$ 177	3756 $\pm$ 239*	3737 $\pm$ 243*	3814 $\pm$ 189*	3750 $\pm$ 208*	3713 $\pm$ 206*	3474 $\pm$ 166*
Peak negative dP/dt (mm Hg/sec)	1917 $\pm$ 124	2210 $\pm$ 150	2178 $\pm$ 129	2113 $\pm$ 95	2223 $\pm$ 199	2177 $\pm$ 120	2202 $\pm$ 136

Values are mean  $\pm$  SEM.

\* $p < 0.001$  vs control; † $p < 0.05$  vs control; ‡ $p < 0.01$  vs control.

stenosis was significantly reduced to  $16.8 \pm 3.2$  cc/min compared to both the resting control state and during isoproterenol infusion in the nonstenotic state.

Figs. 1 and 2 demonstrate the relation between regional shortening and coronary blood flow for part A. This relation was best described by a curvilinear polynomial function,  $y = -23.1 + 2.94x - 0.008x^2$ ;  $r = 0.72$ ,  $p < 0.0001$ , where  $y$  is fractional shortening and  $x$  is blood flow, both expressed as a percentage of control values. This curve fit was superior to either linear or logarithmic fits within the range of observations made. Extrapolation beyond this range into higher flow ranges would predict a decrease in regional function, which is clearly not physiologic.

Thus, the interpretation of the data within the observed range is that there is a relatively flat relation between flow and function in the high flow ranges and a more linear fall below 100% of control flows.

**Part B.** Table IV summarizes the hemodynamic responses to isoproterenol infusion in the presence and absence of coronary stenoses that impaired reactive hyperemia but not resting coronary blood flow. Comparable degrees of tachycardia, decrease in mean blood pressure, and increase in peak positive rate of change of left ventricular pressure (dP/dt) were induced by isoproterenol in the presence and absence of coronary stenoses.

Table V summarizes the blood flow and coronary

**Table V.** Coronary flow parameters of the ischemic zone at rest and during isoproterenol infusions in the presence and absence of coronary stenoses: Part B

	No stenosis	Stenosis 1	Stenosis 2	Stenosis 3	Stenosis 4	Stenosis 5
Coronary flow reserve						
Rest	3.70 ± 0.26	2.84 ± 0.21*	2.53 ± 0.16*	2.01 ± 0.12*	1.63 ± 0.11*	1.11 ± 0.05*
% of control	—	68.2 ± 5.1	56.8 ± 4.1	39.2 ± 4.5	23.6 ± 4.5	4.1 ± 1.9
Coronary blood flow (ml/min)						
Rest	41.7 ± 4.1	41.7 ± 4.9	40.5 ± 4.3	40.6 ± 4.8	40.9 ± 5.5	38.2 ± 4.1
Isoproterenol	58.6 ± 7.6†	56.9 ± 8.5†	54.8 ± 7.4†	50.2 ± 6.6†	50.2 ± 7.7†	34.3 ± 4.9*
% of control	148 ± 10	141 ± 10	135 ± 7	126 ± 8	123 ± 10	85 ± 3*

Values are mean ± SEM.

\**p* < 0.001 vs no stenosis; †*p* < 0.01 vs rest; coronary flow reserve values, expressed as percentage of control, all differ from each other at the *p* < 0.01 level except for stenosis 1 and 2, which are different at the *p* < 0.05 level (Tukey's test, see text).

**Table VI.** Regional function parameters at rest and during isoproterenol infusions in the presence and absence of coronary stenoses: Part B

	Control	No stenoses	Isoproterenol infusion (0.25 µg/kg/min)				
			Stenosis 1	Stenosis 2	Stenosis 3	Stenosis 4	Stenosis 5
Ischemic zone							
End-diastolic segment length (mm)	9.9 ± 0.4	9.6 ± 0.5	9.5 ± 0.6	9.6 ± 0.5	9.6 ± 0.5	9.5 ± 0.6	9.7 ± 0.6
End-systolic segment length (mm)	7.9 ± 0.5	6.5 ± 0.6*	6.6 ± 0.6*	6.7 ± 0.6*	6.7 ± 0.6*	6.6 ± 0.6*	7.1 ± 0.6*
Fractional shortening (%)	20.3 ± 2.3	32.6 ± 3.9*	31.0 ± 3.6*	31.0 ± 3.7*	30.6 ± 3.6*	30.6 ± 3.6*	27.5 ± 3.4*,†
Fractional shortening (% of control)	—	162 ± 12	155 ± 11	155 ± 11	152 ± 10	153 ± 11	136 ± 10‡
Nonischemic zone							
End-diastolic segment length (mm)	10.1 ± 0.8	9.4 ± 0.7*	9.4 ± 0.7*	9.6 ± 0.7	9.4 ± 0.7*	9.4 ± 0.7*	9.5 ± 0.7§
End-systolic segment length (mm)	8.7 ± 0.7	7.4 ± 0.6*	7.4 ± 0.6*	7.4 ± 0.6*	7.4 ± 0.5*	7.4 ± 0.5*	7.3 ± 0.5*
Fractional shortening (%)	13.9 ± 0.9	21.2 ± 2.3*	20.9 ± 2.8*	21.8 ± 2.9*	21.0 ± 2.9*	21.2 ± 2.9*	22.2 ± 3.1*
Fractional shortening (% of control)	—	167 ± 17	164 ± 22	173 ± 26	158 ± 16	165 ± 23	175 ± 26

Values are mean ± SEM.

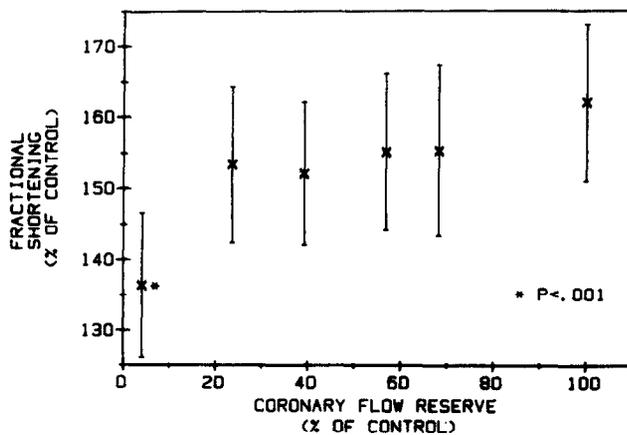
\**p* < 0.001 vs control; †*p* < 0.01 vs no stenosis; ‡*p* < 0.001 vs no stenosis; §*p* < 0.01 vs control.

flow reserve results. Coronary flow reserve at rest was 3.70 ± 0.26, and each stenosis showed a progressive impairment of this parameter. For stenosis No. 5 coronary flow reserve was 1.11 ± 0.05 or 4.1 ± 1.9% of control values signifying near-total loss of reactive hyperemia. Resting coronary blood flow was stable throughout the protocol.

Table VI summarizes the regional function results at control levels and during isoproterenol infusion. Shortening increased in the absence of a stenosis from 20.3 ± 2.3 to 32.6 ± 3.9% (*p* < 0.001). For stenoses Nos. 1 to 4, the shortening remained at this elevated level. With stenosis No. 5, shortening was

significantly lower (27.5 ± 3.4%) than during infusion in the absence of a stenosis (*p* < 0.01) but was still greater than the resting control shortening (*p* < 0.001).

From Table V, it is evident that the degree of hyperemia induced by isoproterenol was less than that produced by the brief coronary occlusion at rest for each stenosis group except stenosis No. 5. For this last group, flow was not significantly different from the resting control flow as predicated by the experimental design. Regional dysfunction was noted only in the latter group. Moreover, the degree of hyperemia during isoproterenol infusion was rela-



**Fig. 3.** Relation between coronary flow reserve and fractional shortening during isoproterenol infusion is shown (part B). Significant deterioration occurred only in the face of near absence of coronary flow reserve. Values are mean  $\pm$  SEM;  $n = 9$ . \* $p < 0.001$  vs nonstenotic control state.

tively similar for stenoses Nos. 1 to 4. This is in keeping with a rather constant metabolic demand induced by the isoproterenol, which did not exhaust vasodilator reserve until stenosis No. 5, even though flow reserve as assessed by the more maximal stimulus of coronary occlusion at rest clearly unveiled the potential functional impairment of flow within each stenosis group.

Fig. 3 demonstrates the relation between regional function during isoproterenol infusion and resting coronary flow reserve. Regional function showed significant deterioration relative to the nonstenotic state only when coronary flow reserve was virtually absent. Note, however, that this level of regional shortening was still above resting control values.

## DISCUSSION

The results of this experiment demonstrate that, in the presence of near-critical coronary stenoses, isoproterenol can elicit relative regional dysfunction, but that with less severe impairments of coronary flow reserve, regional function is maintained relative to resting control values. Moreover, despite impairments of the maximal increase in postocclusion coronary flow, the stress of the isoproterenol infusion failed to exhaust vasodilator reserve except with the most severe stenoses. This suggests that the clinical use of this drug to elicit regional dysfunction will not be sensitive in detecting patients with mild or moderate lesions.

**Clinical studies.** Several clinical investigations of the effects of isoproterenol have been reported. Krasnow et al.<sup>21</sup> studied a heterogeneous group of patients, including coronary patients, and noted angina induction in only two subjects. Coronary flow

increased by 72% and only one patient demonstrated actual reversal of arteriovenous lactate differences in coronary sinus samples. Cohen et al.<sup>22</sup> extended these observations in a group of patients with a broad range of angiographically documented coronary diseases. By means of indicator dilution methods, they showed that isoproterenol caused remarkably similar increases in coronary flow in both normal subjects and in coronary patients, whereas analysis of lactate metabolism demonstrated clear abnormalities in the majority of coronary subjects. Wexler et al.<sup>23</sup> showed that isoproterenol infusion caused no ECG abnormalities in normal subjects, whereas ST segment and T wave abnormalities were commonly induced in patients with prior myocardial infarction. However, no chest pain was induced in this study. Combs and Martin<sup>24</sup> performed a similar study in 20 patients with more than a 50% diameter reduction of a major coronary branch and in 15 patients judged to have normal coronary arteries. Twelve of 20 (60%) coronary patients manifested abnormal ECG findings during the infusion. Manca et al.<sup>25</sup> used the presence of at least one 75% stenosis on the cineangiogram to designate the presence of significant coronary disease and found a 70% sensitivity for detection of these patients when isoproterenol-induced ECG abnormalities were present. Horowitz et al.<sup>26</sup> used direct coronary injections of Xe<sup>133</sup> to estimate coronary flow response to isoproterenol. In contrast to the study of Cohen et al.,<sup>22</sup> these investigators found that nearly all patients increased coronary flow, but this hyperemic response was markedly attenuated in patients with angiographically defined stenoses of at least 70% diameter reduction. Only one patient developed chest pain. Similarly, Horowitz et al.<sup>27</sup> noted a general but highly variable decrement in isoproterenol-induced hyperemia in relation to angiographic severity of coronary lesions and presence or absence of collaterals. These prior clinical investigations are limited in several ways with respect to the objectives of this current study. First, there was a marked heterogeneity in patient groups, which frequently included patients with total obstructions or prior infarctions and resting wall motion abnormalities. Second, it is difficult to determine from historic or angiographic data which patients had subcritical or critical coronary lesions<sup>4</sup> and, therefore, the studies do not allow conclusions as to how useful the technique is in identifying patients with mild disease. Third, no assessment of regional function during the isoproterenol stress was undertaken. And, finally, none gives information regarding resting coronary flow reserve as a means of identifying the severity of coronary lesions.

**Experimental studies.** Several animal investigations are important to consider. Daniell et al.<sup>15</sup> studied the effects of injections of isoproterenol on coronary blood flow and myocardial function in dogs. They described a triphasic response of coronary blood flow characterized by an initial rise, a sharp drop caused by decreased coronary perfusion pressure, and then a sustained rise in blood flow as perfusion pressure rose slightly and then stabilized. They showed that ventricular force generation, as measured by a strain gauge, largely paralleled this pattern of coronary flow. Moreover, during the phase when coronary flow fell to control levels, ventricular force generation remained at or above preisoproterenol levels despite evidence of anaerobic metabolism.

Griggs et al.<sup>16</sup> determined that the epicardial and endocardial lactate/pyruvate ratios were similar during control and isoproterenol-stimulated states in the absence of coronary stenoses. In contrast, subendocardial lactate/pyruvate ratios rose with partial constriction of left main coronary artery flow during isoproterenol infusion. The constriction did not impair basal coronary flow, but flow during the infusion rose by only 61% compared to a 115% increase in the absence of a stenosis. Although this demonstrated a relative supply-demand imbalance in the subendocardium, neither regional function nor resting coronary flow reserve was documented.

Buckberg and Ross<sup>17</sup> demonstrated that very high doses of isoproterenol could induce relative underperfusion of the subendocardium even in the absence of coronary stenoses. Epicardial coronary flow, subendocardial/epicardial flow ratios, and coronary perfusion pressure paralleled the observed regional contractile function as measured by strain gauges. Thus, initial increases in flow and function were followed at higher doses of isoproterenol by a progressive decrease in each parameter but of note is that contractile function always remained above control levels despite relative underperfusion of the subendocardium.

Vatner et al.<sup>30,31</sup> studied the effects of isoproterenol on normal and ischemic myocardium in conscious dogs. The ischemic model in one study<sup>29</sup> consisted of left main coronary artery constriction resulting in global ischemia with an average 30% decrease in epicardial coronary blood flow, significant cardiac enlargement, and deterioration of velocity of fiber shortening. In this severely ischemic model, administration of isoproterenol caused additional deterioration of ventricular function. In another study,<sup>31</sup> the effects of isoproterenol in the presence of only regional ischemia were determined. In contrast to the prior investigation, isoproterenol

improved overall left ventricular function. More important, despite deterioration of function in severely ischemic segments with isoproterenol, all moderately ischemic zones and most "border zone" segments showed improvement in function despite preinfusion coronary flows of approximately 65% and 90% of control values, respectively. Furthermore, despite a depressed velocity of postocclusion shortening, an increase in function was noted during isoproterenol infusion that paralleled a rise in blood flow to these regions. The return of function exceeded preocclusion levels in the border zone and approximated preocclusion levels in the moderately ischemic zone. In contrast, in the central severely ischemic zone, function showed further deterioration when there was no associated increase in coronary flow. The authors concluded that a strong inotropic agent can improve regional function, even in the ischemic myocardium, as long as additional blood flow can be provided through either primary or collateral channels.

Battler et al.<sup>19</sup> proposed that isoproterenol could be used to detect "latent" coronary stenoses by evocation of regional dysfunction and ECG abnormalities. Stenoses were created by inflating a hydraulic occluder until mild reduction of systolic wall thickening occurred and deflating it slightly until wall function returned to normal. By means of very small doses of isoproterenol, marked regional dysfunction and ECG abnormalities were demonstrated. These findings are surprising considering the references cited previously, and several factors may have contributed to these dramatic results. First, information regarding coronary flow was not provided in this study and, thus, it is unknown if impairment of resting flow was present. Second, the infusion may have caused a large decrease in both coronary perfusion pressure and coronary flow.<sup>15,17</sup> Finally, the hydraulic occluder may have partially collapsed, increasing the severity of stenosis and further aggravating a decrease in coronary blood flow.<sup>32,33</sup> Thus, in the absence of hemodynamic and blood flow data, it is unclear if these stenoses were truly "latent" or comparable to the subcritical stenoses studied in the current investigation.

Gallagher et al.<sup>20</sup> extended these observations by means of two levels of coronary stenoses created in a similar way. They demonstrated that regional function deteriorated below what was observed both at rest and during isoproterenol infusion in the absence of a stenosis. This occurred despite maintenance of mean transmural myocardial blood flow (microsphere technique) at resting levels. The mildest stenosis was characterized by preservation of some epicardial flow reserve and abolition of midmyocar-

dial and subendocardial flow reserve during isoproterenol stimulation. The more severe stenosis showed additional loss of subepicardial flow reserve during isoproterenol infusion. Several important differences between that study and the current investigation deserve emphasis. First, the effects of the stenosis on epicardial coronary blood flow and coronary flow reserve were not assessed. Second, although regional function was not impaired at rest, some embarrassment of basal epicardial coronary flow may have been present if one considers the curvilinear relation between epicardial flow and regional function.<sup>34</sup> This might not be detected by the microsphere technique which assesses both direct and indirect (collateral) flow. Third, the finding that coronary flow during infusion was equal to instead of greater than resting coronary flow suggests that the stenoses might have been associated with a restriction of resting epicardial flow.<sup>13-19, 21, 22, 26, 30-33</sup> Moreover, maintenance of subepicardial reserve with coronary stenoses characterized by mild but significant reductions of basal epicardial coronary flow has been previously documented.<sup>35</sup> This is also implied by the work of Gould et al.,<sup>36</sup> who demonstrated that flow reserve is not totally abolished until resting epicardial flow has decreased. Finally, several investigators<sup>37-39</sup> have demonstrated that epicardial flow measurements are generally lower than measures of transmural myocardial blood flow under conditions of vasodilation, and this is probably secondary to enhanced epicardial collateral blood flow. Thus, it is likely that the two "latent" stenoses in the study of Gallagher et al.<sup>20</sup> were much more severe than the most severe "subcritical" stenosis (stenosis no. 5, part B) in this current study. The current study, therefore, concentrates on observations about the potential effects of isoproterenol in a range of mild coronary stenoses that has not been previously studied.

Another important difference is that isoproterenol caused a substantial enhancement of regional shortening in the current study in both the nonischemic bed and in the ischemic zone prior to creation of a stenosis, whereas this was not the case in the study of Gallagher et al.<sup>20</sup> The reasons for this disparity are unclear but may be related to the small sample size in their study. Other investigators, however, have documented increased regional function in response to isoproterenol even in ischemic states.<sup>31</sup> Although dysfunction relative to the nonstenotic group could be detected in the current study, dysfunction below preisoproterenol control levels did not occur. These findings are also in

keeping with the observations of Vatner et al.<sup>31</sup> and others<sup>15-17</sup> and are emphasized by the results shown in Fig. 2, which demonstrate that a fall of function below resting levels was not seen until significant impairments of relative coronary flow were induced.

Prior work from this laboratory has demonstrated that the relation between subcritical impairments of coronary flow reserve and regional dysfunction during stress is altered by the form of stress utilized.<sup>6,7</sup> This relation, in turn, is predominantly influenced by the determinants of coronary blood flow during the stress itself. Rapid atrial pacing, in the setting of subcritical stenoses, reduced regional function below control levels when coronary flow reserve was approximately two or less, whereas no dysfunction was noted when dopamine infusion was investigated.<sup>6,7</sup> Thus, the results of the current investigation are intermediate to those two studies. Moreover, these studies begin to determine the lower limits of flow reserve that may impact upon regional function during stress. Such relationships are important in defining the significance of coronary flow reserve measurements at rest relative to the more traditional indicators of the functional significance of coronary disease during stress testing. It is clear that not all impairments of coronary flow reserve are associated with stress-induced regional dysfunction, although metabolic abnormalities, not measured in this study, may well be present under these circumstances as has been previously shown.<sup>13-16, 21, 22</sup> These factors must be taken into account particularly as methods for detecting mild impairments of coronary flow reserve in patients become more available.<sup>2, 3, 8-12</sup> Furthermore, the results of this and prior studies suggest that the primary determinant of these relationships is the blood flow during the stress itself.

**Limitations.** Several limitations of the current investigation should be considered. Rigid intraluminal stenoses were not used, but care was taken to circumvent potential changes in stenosis severity between the rest and infusion stages with a rigid screw occluder. Transmural myocardial blood flow was not measured because the study was intended to provide data analogous to the clinical assessment of epicardial coronary flow reserve and because all of the stenoses (except the most severe stenosis in part A) were associated with conditions of normal or high epicardial flow when collateral flow would not be expected to be of primary importance. While measurement of subendocardial regional function does provide a good index of the relative adequacy of total subendocardial perfusion,<sup>40</sup> the paucity of

regional dysfunction seen in this study prevents exclusion of some role of collateral flow in the maintenance of regional function despite impairments of coronary flow reserve. This potential problem was likely to be minimal in the acute model in contrast to chronic models of coronary stenosis, which regularly develop large coronary collaterals. The issue, however, does underscore one of the potential limitations of the clinical use of the coronary flow reserve index measured at rest as an adequate, isolated measure of the "functional" significance of coronary stenoses because the determinants of hyperemic coronary perfusion (epicardial and collateral) are quite different during stress compared to resting conditions and may impact dramatically on the ability to detect abnormalities of parameters that reflect functional derangements. These limitations would apply to both single-vessel coronary disease, as modeled in this investigation, and multivessel disease where collateral recruitment under stress may be quite variable. Finally, it is important to establish the adequacy of the stress induced by isoproterenol. The dose used in this study (0.25  $\mu\text{g}/\text{kg}/\text{min}$ ) was similar to that used by Gallagher et al.<sup>20</sup> (0.2  $\mu\text{g}/\text{kg}/\text{min}$ ) slightly less than that used by Vatner et al.<sup>31</sup> (0.4  $\mu\text{g}/\text{kg}/\text{min}$ ), and much greater than that used by Battler et al.<sup>19</sup> (0.02  $\mu\text{g}/\text{kg}/\text{min}$ ) Peak heart rate and blood pressures in this study were greater than in prior investigations,<sup>19, 20, 32</sup> whereas the peak positive  $dP/dt$  values were lower, possibly secondary to the effects of anesthesia. Thus the degree of stress induced in the current study was generally comparable to prior studies in chronically instrumented conscious dog models.

**Conclusions.** There are several clinical implications of this investigation.

1. A diminution in the normal enhancement of regional function caused by isoproterenol can be detected only when coronary reserve is severely impaired. In this investigation, lesions associated with up to an 80% loss of coronary flow reserve were not associated with regional dysfunction. Furthermore, isoproterenol does not induce a fall in regional shortening compared to resting values unless blood flow is severely impaired. This suggests limited clinical efficacy of isoproterenol stress testing in

detecting mild single-vessel coronary disease when wall motion abnormalities are sought.

2. Impairment of coronary flow reserve at rest is a highly sensitive index of the potential significance of a coronary stenosis. Detection of impairment of this index is more sensitive than the detection of regional dysfunction during an isoproterenol challenge.

3. However, the relation between resting impairments of coronary flow reserve and regional dysfunction during stress is predominantly a function of the actual blood flow during the stress itself. Because the determinants of the hyperemic blood flow are markedly different between rest and stress stages, the relation between coronary flow reserve and regional shortening or other indicators of dysfunction during stress will necessarily vary, depending on the type of stress utilized, the presence of coronary disease in other arteries, and the presence or absence of effective collateral flow during the stress itself. Thus, determination of the ultimate "functional" significance of any lesion should not be made solely on the basis of isolated measures of coronary flow reserve at rest, particularly when this index is only mildly impaired, but should also take into account the actual impact of the lesion during physiologic stress.

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