

- Tc-99m-methoxyisobutyl-isonitrile-uptake at rest in patients with myocardial infarcts—comparison with morphological and functional parameters obtained from gradient-echo magnetic resonance imaging. *Eur Heart J* 1994;15:97–107.
25. Baer FM, Voth E, Schneider CA, Theissen P, Schicha H, Sechtem U. Comparison of low-dose dobutamine gradient-echo magnetic resonance imaging and positron emission tomography with [F-18]fluorodeoxyglucose in patients with chronic coronary artery disease: a functional and morphological approach to the detection of residual myocardial viability. *Circulation* 1995;91:1006–1015.
  26. Buser PT, Auffermann W, Holt WW, et al. Noninvasive evaluation of global left ventricular function with use of cine nuclear magnetic resonance. *J Am Coll Cardiol* 1989;13:1294–1300.
  27. Fujita N, Hartiala J, O'Sullivan M, et al. Assessment of left ventricular diastolic function in dilated cardiomyopathy with cine magnetic resonance imaging: effect of an angiotensin converting enzyme inhibitor, benazepril. *Am Heart J* 1993;125:171–178.
  28. Manning F, Morgan-Manning MG. Gated SPECT with technetium-99m-sestamibi for assessment of myocardial perfusion abnormalities. *J Nucl Med* 1993;34:601–608.
  29. Hurwitz G, Schwab M, MacDonald AC, Driedger A. Quantitative analysis of myocardial ischemia on end-diastolic thallium-201 perfusion images. *Eur J Nucl Med* 1990;17:257–263.
  30. Rigo P, Leclercq B, Itti R, Lahiri A, Braat S. Technetium-99m-tetrofosmin myocardial imaging: a comparison with thallium-201 and angiography. *J Nucl Med* 1994;35:587–593.
  31. Higley B, Lahiri A, Elly DJ. Technetium-99m complexes of functionalized diphosphines for myocardial perfusion imaging in man. In: van der Wall EE, Sochor H, Righetti A, Niemeyer MG, eds. *What's new in cardiac imaging: SPECT, PET and MRI*. The Netherlands: Kluwer Academic Publishers; 1992:93–109.
  32. Higley B, Smith FW, Smith T, et al. Technetium-99m 1,2-bis(bis(2 ethoxyethyl) phosphino) ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. *J Nucl Med* 1993;34:30–38.
  33. La Canna G, Alfieri O, Giubbini R, et al. Echocardiography during infusion of dobutamine for the identification of reversible dysfunction in patients with chronic coronary artery disease. *J Am Coll Cardiol* 1994;23:617–626.
  34. Barilla F, Gheorghide M, Alam M, Khaja F, Goldstein S. Low-dose dobutamine in patients with acute myocardial infarction identifies viable but not contractile myocardium and predicts the magnitude of improvement in wall motion abnormalities in response to coronary revascularization. *Am Heart J* 1991;122:1522–1531.
  35. Iskandrian AS, Hakki A, Kane SA, et al. Rest and redistribution thallium-201 myocardial scintigraphy to predict improvement in left ventricular function after coronary artery bypass grafting. *Am J Cardiol* 1983;51:1312–1316.
  36. Gibson RS, Watson DD, Taylor GJ, et al. Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy. *J Am Coll Cardiol* 1983;1:804–815.
  37. Tamaki N, Yonekura Y, Yamashita K, et al. Positron emission tomography using fluorine-18-deoxyglucose in the evaluation of coronary artery bypass grafting. *Am J Cardiol* 1989;64:860–865.
  38. Tillisch JH, Brunken R, Marshall R, et al. Reversibility of cardiac wall motion abnormalities predicted by positron tomography. *N Engl J Med* 1986;314:884–888.
  39. Cuocolo A, Maurea S, Pace L, et al. Resting technetium-99m methoxyisobutyl-isonitrile cardiac imaging in chronic coronary artery disease: comparison with rest-redistribution thallium-201 scintigraphy. *Eur J Nucl Med* 1993;20:1186–1192.
  40. Dilsizian V, Arrighi JA, Diodati JG, et al. Myocardial viability in patients with chronic coronary artery disease. Comparison of <sup>99m</sup>Tc-sestamibi with thallium reinjection and <sup>18</sup>F-fluorodeoxyglucose. *Circulation* 1994;89:578–587.
  41. Udelson JE, Coleman PS, Metherall J, et al. Predicting recovery of severe regional ventricular dysfunction. Comparison of resting scintigraphy with <sup>201</sup>Tl and <sup>99m</sup>Tc-sestamibi. *Circulation* 1994;89:2552–2261.

## Effect of $\beta_1$ Adrenergic Receptor Blockade on Myocardial Blood Flow and Vasodilatory Capacity

Morten Böttcher, Johannes Czernin, Karl Sun, Michael E. Phelps and Heinrich R. Schelbert

*Division of Nuclear Medicine, Department of Molecular and Medical Pharmacology, UCLA School of Medicine, Laboratory of Structural Biology and Molecular Medicine, University of California, Los Angeles, California*

The  $\beta_1$  receptor blockade reduces cardiac work and may thereby lower myocardial blood flow (MBF) at rest. The effect of  $\beta_1$  receptor blockade on hyperemic MBF is unknown. **Methods:** To evaluate the effect of selective  $\beta_1$  receptor blockade on MBF at rest and during dipyridamole induced hyperemia, 10 healthy volunteers (8 men, 2 women, mean age  $24 \pm 5$  yr) were studied using <sup>13</sup>N-ammonia PET (two-compartment model) under control conditions and again during metoprolol (50 mg orally 12 hr and 1 hr before the study). **Results:** The resting rate pressure product ( $6628 \pm 504$  versus  $5225 \pm 807$ ) and heart rate ( $63 \pm 6$ – $54 \pm 5$  bpm) declined during metoprolol ( $p < 0.05$ ). Similarly, heart rate and rate pressure product declined from the baseline dipyridamole study to dipyridamole plus metoprolol ( $p < 0.05$ ). Resting MBF declined in proportion to cardiac work by approximately 20% from  $0.61 \pm 0.09$ – $0.51 \pm 0.10$  ml/g/min ( $p < 0.05$ ). In contrast, hyperemic MBF increased when metoprolol was added to dipyridamole ( $1.86 \pm 0.27$ – $2.34 \pm 0.45$  ml/g/min;  $p < 0.05$ ). The decrease in resting MBF together with the increase in hyperemic MBF resulted in a significant increase in the myocardial flow reserve during metoprolol ( $3.14 \pm 0.80$ – $4.61 \pm 0.68$ ;  $p < 0.01$ ). **Conclusion:** The  $\beta_1$  receptor blockade increases coronary vasodilatory capacity and myocardial flow reserve. However, the mechanisms accounting for this finding remain uncertain.

**Key Words:** myocardial blood flow; myocardial flow reserve;  $\beta_1$  receptor blockade; PET

**J Nucl Med 1997; 38:442–446**

Myocardial  $\beta_1$  receptors modulate heart rate, systolic blood pressure and myocardial contractility in response to adrenergic

stimulation. Blockade of myocardial  $\beta_1$  receptor activity reduces myocardial oxygen requirements and myocardial blood flow (1). The beta blocker-induced reduction in myocardial oxygen demand has been used successfully in the treatment of chronic and acute coronary artery syndromes (2,3). The beta-receptor blockade might also alter myocardial blood flow during near maximal coronary vasodilation. This is, because beta-receptor blockade reduces myocardial contractility that may reduce extravascular resistive forces. Such forces have been demonstrated to impede coronary blood flow during pharmacological vasodilation (4). On the other hand, the reduction in heart rate associated with  $\beta_1$ -receptor blockade results in an increased duration of the diastolic coronary flow phase that may result in increases in hyperemic blood flow (5).

However, the net effect of such intervention on hyperemic blood flow and myocardial flow reserve have not been quantified in humans. This can now be accomplished with dynamic PET and <sup>13</sup>N-ammonia as a tracer of myocardial blood flow (6–9). The aim of this study was, therefore, to quantify noninvasively with <sup>13</sup>N-ammonia PET the effect of  $\beta_1$ -receptor blockade on myocardial blood flow and vasodilatory capacity in humans.

### STUDY POPULATION

The study population consisted of 10 healthy volunteers (8 men, 2 women, mean age  $24 \pm 5$  yr) with a low likelihood for coronary artery disease, as evidenced by a normal physical examination, normal resting ECG and absence of any significant risk factors (10). None of the participants had a history of cigarette smoking, elevated serum cholesterol levels, hypertension or diabetes and none was on any medication. To avoid

Received Mar. 7, 1996; revision accepted Jun. 15, 1996.

For correspondence or reprints contact: Johannes Czernin, MD, Dept. of Molecular and Medical Pharmacology, UCLA School of Medicine, 10833 LeConte Ave., Los Angeles, CA 90095-6948.

**TABLE 1**  
Hemodynamic Findings

Patient no.	Systolic blood pressure (mmHg)				Diastolic blood pressure (mmHg)				Heart rate (bpm)						
	Rest	Rest + beta		Dipyridamole + beta		Rest	Rest + beta		Dipyridamole + beta		Rest	Rest + beta		Dipyridamole + beta	
		blocker	Dipyridamole	blocker	Dipyridamole		blocker	Dipyridamole	blocker	Dipyridamole		blocker	blocker	Dipyridamole	blocker
1	101	82	111	97	60	52	66	60	57	43	97	68			
2	98	91	103	94	56	51	57	53	60	50	86	72			
3	115	110	116	107	59	51	60	48	56	55	77	67			
4	103	93	115	98	55	51	58	54	69	61	107	96			
5	93	98	88	105	64	54	42	56	74	56	105	83			
6	107	93	115	109	68	50	57	48	62	49	93	82			
7	119	114	113	126	68	64	64	60	60	54	84	89			
8	108	96	109	108	54	53	62	58	66	59	100	92			
9	105	99	116	110	61	57	56	64	61	55	90	94			
10	108	97	110	106	59	53	60	54	64	53	95	86			
mean $\pm$ s.d.	106 $\pm$ 8	97 $\pm$ 9*	110 $\pm$ 9	106 $\pm$ 9	60 $\pm$ 5	54 $\pm$ 4*	58 $\pm$ 7	56 $\pm$ 5	63 $\pm$ 6	54 $\pm$ 5*	93 $\pm$ 9	83 $\pm$ 11*			

\*p < 0.05 versus baseline

untoward side effects of dipyridamole, individuals with bronchial asthma were excluded from the study.

All study participants refrained from intake of caffeine-containing food or beverages for at least 24 hr before each study (9). All participants gave written informed consent as approved by the local human subject protection committee (11,12).

### Study Protocol

The two-day study protocol consisted of four  $^{13}\text{N}$ -ammonia PET blood flow measurements. On one day, myocardial blood flow was studied at rest and during dipyridamole-induced hyperemia under control conditions. On the other day, this sequence was repeated after treatment with 50 mg metoprolol orally 12 hr and 1 hr before the study. The study sequence was performed in a random order with a mean difference of 9 days (range 3–19 days) between the two studies.

### PET

The Siemens/CTI 931/08-12 positron tomograph, which acquires 15 transaxial images simultaneously, was used. This device has an axial field of view of 10 cm, an intrinsic in-plane spatial resolution of 6.5 mm FWHM and an interplane spacing of 6.7 mm. The transaxial images were reconstructed using a Shepp filter with a cutoff frequency of 0.3 Nyquist, resulting in an effective in-plane resolution of 11 mm FWHM (13).

After a 20-min transmission image to correct for photon attenuation,  $^{13}\text{N}$ -ammonia (20 mCi) was injected and the dynamic imaging sequence was started simultaneously. Fifty minutes later, to allow for decay of the radio tracer activity, pharmacological vasodilation was induced by intravenous infusion of dipyridamole for 4 min (0.56 mg/kg). Four minutes, thereafter,  $^{13}\text{N}$ -ammonia (20 mCi) was injected and serial imaging commenced. The dynamic imaging protocol consisted of twelve 10-sec, two 30-sec, one 60-sec and one 15-min images.

Throughout the flow studies, heart rate and blood pressure (automated cuff measurements) were measured at 1-min intervals. The rate pressure product was calculated from the two measurements during the first 2 min of the  $^{13}\text{N}$ -ammonia image acquisition. Mean arterial blood pressure was calculated as (systolic blood pressure + (2  $\times$  diastolic blood pressure))  $\div$  3.

### Quantification of Blood Flow

The serially-acquired sets of 15 transaxial images were reoriented into six short-axis planes as described previously (14,15). The short-axis images were used to generate polar maps of the  $^{13}\text{N}$ -ammonia activity distribution and compared to a database of

normals to ascertain that all participants were indeed free of coronary artery disease (14).

MBF was quantified in the vascular territories of the left anterior descending artery, left circumflex and the right coronary artery, as described previously (16–18).

ROIs were approximated to the three vascular territories on three short-axis images (one basilar, one midventricular and one apical image). These regions encompass 70–90° sections of the left ventricular myocardium, as described previously (19). The same anatomical landmark (the insertion of the right ventricle into the interventricular septum) was used in all studies to ensure identical ROIs in all four blood flow studies.

A small ROI was centered in the left ventricular blood pool to derive the arterial input function (20). The regions were then copied to the first 120 sec of the dynamic imaging sequence to obtain tissue time-activity curves.

For each of the vascular territories, the three tissue curves (basilar, midventricular and apical) were averaged and corrected for partial volume effects by assuming a uniform myocardial wall thickness of 1 cm (21). Both the blood-pool and myocardial time-activity curves were corrected for physical decay. They were then fitted with a previously validated two-compartment model that corrects for spillover of activity from blood pool into the left ventricular myocardium (8,15,22).

### Statistical Analysis

Mean values are given with their s.d.s. The paired Student's *t*-test was used to determine differences within each individual. Slopes and intercepts of regression lines were compared using the analysis of covariance. Correlations were sought using least squares method. Probability values of less than 0.05 were considered significant.

## RESULTS

### Hemodynamic Findings

The hemodynamic findings are listed in Table 1. The resting rate pressure product declined from 6628  $\pm$  504 at control to 5225  $\pm$  807 (p < 0.05) during metoprolol. A decline in rate pressure product was observed in all but one participant and was due to reductions in both heart rate (63  $\pm$  6 versus 54  $\pm$  5 bpm; p < 0.05) and systolic blood pressure (106  $\pm$  8 versus 97  $\pm$  9 mmHg; p < 0.05).

Similarly, the dipyridamole-induced increase in rate pressure product was attenuated after treatment with metoprolol

**TABLE 2**  
Myocardial Blood Flow (MBF) and Flow Reserve

Patient No.	Rest MBF (ml/g/min)		MBF/RPP ( $\times 10.5$ )		Hyperemic MBF (ml/g/min)		Flow reserve	
	Baseline	Beta blocker	Baseline	Beta blocker	Baseline	Beta blocker	Baseline	Beta blocker
1	0.46	0.44	7.99	12.48	2.12	1.91	4.61	4.34
2	0.53	0.35	9.01	7.69	1.55	1.82	2.92	5.20
3	0.58	0.47	9.01	7.77	1.89	2.36	3.26	5.02
4	0.65	0.52	9.15	9.17	1.68	1.90	2.58	3.65
5	0.66	0.51	9.59	9.29	1.79	2.11	2.71	4.14
6	0.55	0.50	8.29	10.97	2.33	2.58	4.24	5.16
7	0.64	0.50	8.96	8.12	1.50	2.11	2.34	4.22
8	0.81	0.71	11.36	12.54	1.72	3.06	2.12	4.31
9	0.61	0.51	9.52	9.37	1.87	3.01	3.07	5.90
10	0.60	0.61	8.68	11.87	2.13	2.54	3.55	4.16
mean $\pm$ s.d.	0.61 $\pm$ 0.09	0.51 $\pm$ 0.10*	9.16 $\pm$ 0.92	9.93 $\pm$ 1.90	1.86 $\pm$ 0.27	2.34 $\pm$ 0.45*	3.16 $\pm$ 0.80	4.61 $\pm$ 0.68*

\*p < 0.05 versus baseline.

MBF/RPP = myocardial blood flow normalized to rate pressure product; mean  $\pm$  s.d. = (syst + (2  $\times$  diast)  $\div$  3)

(10208  $\pm$  1076 versus 8575  $\pm$  1770; p < 0.05). However, the mean aortic blood pressure during hyperemia was similar under control conditions and after metoprolol (75  $\pm$  7 versus 72  $\pm$  5 mmHg; p = ns).

### Myocardial Blood Flow and Flow Reserve

Resting myocardial blood flow declined in proportion to cardiac work by approximately 20% from 0.61  $\pm$  0.09 to 0.51  $\pm$  0.10 ml/g/min (p < 0.05) (Table 2; Fig. 1A). Overall, resting blood flow was linearly related to the rate pressure product (y = 0.13 + 0.00007x; r = 0.66; p < 0.005) (Fig. 2).

To account for differences in rate pressure product (an index of cardiac work) between patients, resting blood flow was normalized to the rate pressure product. Normalized resting myocardial blood flow ( $\times 10^5$ ) work did not change from control to  $\beta_1$  receptor blockade (9.16  $\pm$  0.92 versus 9.93  $\pm$  1.90; p = ns) (Table 2) suggesting a proportional decline in blood flow and rate pressure product during  $\beta_1$ -receptor blockade. The association between the rate pressure product and myocardial blood at rest was analyzed also for individuals under baseline conditions and during metoprolol using analysis of covariance. Such analysis revealed: (a) a significant correlation between rate pressure product and blood flow under baseline conditions (y = -0.38 + 0.00015x, p = 0.0052); (b) no significant correlation between rate pressure product and myocardial blood flow during  $\beta_1$  receptor blockade (y = 0.27 + 0.00047x; r = 0.39; p = ns); and (c) no significant F ratio (1.409; p = 0.27311) indicating that the slopes or intercepts do not differ for those relationships.

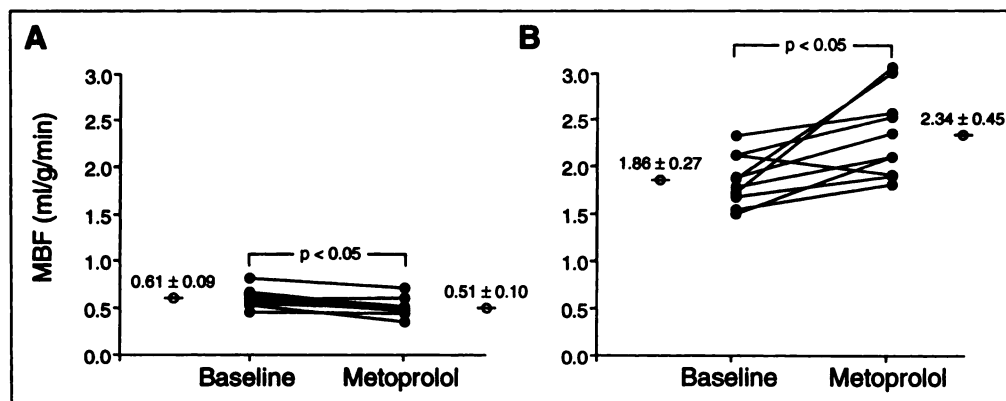
Hyperemic myocardial blood flow increased from 1.86  $\pm$  0.27 ml/g/min during control to 2.34  $\pm$  0.45 ml/g/min during dipyridamole combined with metoprolol (p < 0.05) (Fig. 1B, Table 2). However, no significant relationship between heart rate and dipyridamole-induced hyperemic blood flow was observed under baseline conditions or during metoprolol (y = 0.8 + 0.019; r = 0.45; p = ns).

The decrease in resting blood flow together with the increase in hyperemic blood flow during  $\beta_1$ -receptor blockade resulted in a significant increase in the myocardial flow reserve, defined as the ratio of hyperemic over resting myocardial blood flow (3.14  $\pm$  0.80 to 4.61  $\pm$  0.68; p < 0.01) (Table 2).

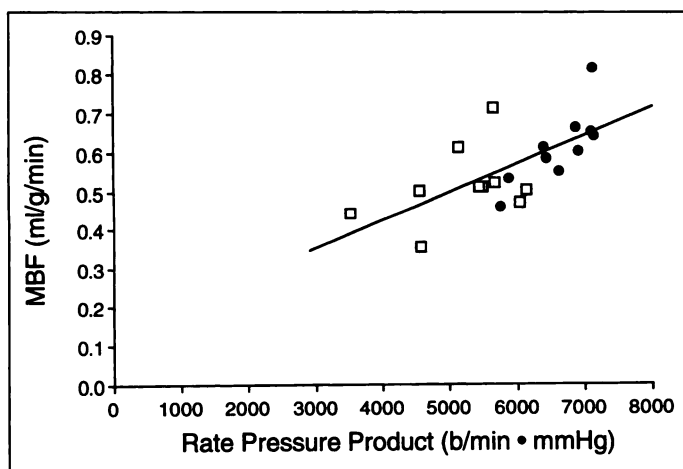
To correct for differences in mean arterial blood pressure, as an index of coronary driving pressure, an index of coronary vascular resistance was derived from the ratio of mean arterial blood pressure to blood flow (mmHg/ml/g/min). This index at rest did not differ between control and metoprolol under resting conditions (127  $\pm$  20 versus 137  $\pm$  25 mmHg/ml/g/min; p = ns). However, minimal coronary resistance declined from 41  $\pm$  7 mmHg/ml/g/min during dipyridamole to 32  $\pm$  5 mmHg/ml/g/min during dipyridamole + metoprolol (p < 0.05).

### DISCUSSION

This study demonstrates that  $\beta_1$ -receptor blockade modulates both resting and hyperemic blood flow. Proportional reductions in cardiac work and myocardial blood flow at rest and increases in hyperemic blood flow resulted in a significant increase in the myocardial flow reserve during  $\beta_1$ -receptor blockade.



**FIGURE 1.** Changes in myocardial blood flow (A) at rest and (B) during dipyridamole-induced hyperemia as induced by  $\beta_1$ -receptor blockade with metoprolol. Metoprolol-induced significant decreases in resting and significant increases in hyperemic blood flow.



**FIGURE 2.** Relationship between myocardial blood flow and rate pressure product (bpm  $\times$  mmHg) under baseline conditions (closed circles) and during metoprolol (open squares). A significant correlation was observed under baseline conditions ( $y = -0.38 + 0.00015x$ ,  $p = 0.0052$ ) but not during  $\beta_1$ -receptor blockade ( $y = 0.27 + 0.00047x$ ;  $r = 0.39$ ;  $p = \text{ns}$ ). A comparison between the slopes and intercepts of the regression lines by analysis of covariance revealed no significant F ratio (1.409;  $p = 0.27311$ ), indicating that the slopes or intercepts do not differ for these relationships.

### Myocardial Blood Flow at Rest

Resting myocardial blood flow, commonly referred to as auto-regulated blood flow, correlates with myocardial oxygen consumption and is determined primarily by left ventricular wall stress, myocardial contractility and heart rate (23–25). However, the rate pressure product is correlated to myocardial oxygen consumption and, therefore, can be used as a simple index of cardiac work (26). As myocardial blood flow is closely linked to myocardial oxygen consumption, the rate pressure product would be expected to be correlated to myocardial blood flow. In fact, a significant relationship between these two parameters has been demonstrated previously in healthy individuals and patients with heart disease (18,19,26–28). Selective  $\beta_1$ -receptor blockade lowers heart rate, contractility and left ventricular wall stress by inhibiting the  $\beta_1$ -receptor mediated positive inotropic and chronotropic effects of norepinephrine. Thus,  $\beta_1$ -receptor blockade reduces the rate pressure product. Accordingly, this antagonistic effect at the receptor level reduced the rate pressure product and coronary blood flow in 17 patients with coronary artery disease by 10%–15% (29). A similar magnitude of changes was observed in the current study. Myocardial blood flow ( $16\% \pm 10\%$ ) and the rate pressure product declined proportionally by  $21\% \pm 9\%$ .

Interestingly, the relationship between rate pressure product and myocardial blood flow was not affected by selective blockade of myocardial  $\beta_1$  receptors. Resting blood flow normalized to the rate pressure product did not differ between control conditions and during metoprolol. Furthermore, analysis of covariance failed to demonstrate a significant F ratio (1.409;  $p = 0.27$ ), indicating that the slopes or intercepts of the regression lines for the relationship between rate pressure product and myocardial blood at rest and during metoprolol did not differ.

A significant correlation between rate pressure product and resting blood flow was only observed under baseline conditions but not during metoprolol. This is likely explained by the narrow range of rate pressure products during  $\beta_1$ -receptor blockade. The similar slopes of the regression lines suggest, that  $\beta_1$ -receptor blockade does not affect significantly the relationship between myocardial blood flow and cardiac work. However, because of the small number of observations, even a

negative analysis of covariance does not rule out entirely a modest effect of  $\beta_1$ -receptor blockade on this relationship.

### Myocardial Blood Flow During Dipyridamole-Induced Hyperemia

Hyperemic myocardial blood flow is modulated by coronary driving pressure (30), heart rate (5) and extravascular compressive forces (4). In addition, the baseline vasomotor tone of the resistance vessels may affect the coronary vasodilatory capacity.

Mean aortic blood pressure, as an index of coronary driving pressure, remained unchanged from baseline to metoprolol. Therefore, the increase in hyperemic blood flow cannot be ascribed to changes in coronary driving pressure.

The heart rate response to dipyridamole was blunted during metoprolol. Such reduction extends the diastolic coronary-filling time that may have contributed to the increase in hyperemic blood flow. However, no significant relationship between heart rate and dipyridamole-induced hyperemic blood flow was observed ( $y = 0.8 + 0.019x$ ;  $r = 0.45$ ;  $p = \text{ns}$ ). Similarly, no significant relationship was observed when the baseline hyperemic data were combined with the hyperemic blood flow during metoprolol. Consistently, much larger changes in heart rate than those observed in the current study were required to alter coronary blood flow in animal experimental studies (31). Thus, a significant contribution of the blunted heart rate response to the increased hyperemic blood flow seems unlikely.

Reductions in extravascular resistive forces may serve as another explanation for the increase in hyperemic blood flow during metoprolol. These forces are determined by physical compression of the intramural coronary arteries and by shear forces that twist coronary arteries as the heart contracts (4). Marzilli et al. (4) demonstrated that extravascular resistive impede coronary blood flow particularly during pharmacological vasodilation. However, these forces can be modulated substantially by changes in left ventricular contractility (4). A similar effect has been demonstrated recently in humans. In healthy individuals, increases in extravascular compressive forces as induced by exercise-attenuated adenosine induced hyperemic myocardial blood flow by 18% (32). However, systolic myocardial compression would only explain a rather small fraction of the increases in diastolic coronary blood flow. As another explanation, beta blocker-induced improvements in diastolic relaxation might have contributed to the improved vasodilatory capacity during metoprolol. Both negative inotropic effects and improved diastolic relaxation may, therefore, have reduced extravascular compressive forces during  $\beta_1$ -receptor blockade. Extravascular compressive forces affect the endocardium of the left ventricle to a greater degree than the epicardium. Yet only the net effect of extravascular compressive forces on myocardial blood flow, but not differential effects on different layers of the myocardium, can be addressed adequately with PET.

The mechanisms underlying the improved coronary vasodilatory capacity during  $\beta_1$ -receptor blockade cannot be elucidated from the current observations. Nevertheless, reductions in extravascular compressive forces, improved diastolic left ventricular relaxation and the blunted heart rate response may have affected beneficially the diastolic phase of myocardial perfusion during dipyridamole-induced hyperemia.

### Study Limitations

This study did not explore the effects of  $\beta_1$ -receptor blockade on resting and hyperemic blood flow in patients with coronary artery disease. Thus, it is unknown whether similar increases in

hyperemic blood flow would have been observed in patients. However, reductions in  $\beta_1$ -adrenergic activity also reduce left ventricular contractility in patients with coronary artery disease. Therefore, we would anticipate similar effects in these patients.

As another limitation, the mechanisms underlying the  $\beta_1$ -receptor blocker induced improved flow reserve cannot be elucidated from the current study. For instance, it can only be speculated that extravascular compressive forces account for the improved coronary vasodilatory capacity. Moreover, extravascular compressive forces affect the endocardial layer of the heart to a greater degree than the epicardial layer. The limited spatial resolution of PET precludes differentiating between the effects of  $\beta_1$ -receptor blockade on endocardial and epicardial blood flow.

As a technical limitation, automated blood pressure measurements may induce some error in the estimation of mean arterial blood pressure. However, such error was likely to have affected all participants to a similar degree. Moreover, the significant relationship between rate pressure product and blood flow at rest argues for the validity of these measurements.

As another technical limitation, the left ventricular wall thickness was assumed to be uniformly 1-cm thick for correction of partial volume effects. It is acknowledged that such simplification may result in systematic errors of flow estimates. Yet, because each participant served as their own control, this assumption does not invalidate the finding of a marked increase in hyperemic blood flow after  $\beta_1$ -receptor blockade. However, it should be noted that more accurate corrections for partial volume effects would be required to quantify the effects of  $\beta_1$ -receptor blockade on myocardial blood flow in patients with coronary artery disease, myocardial infarctions and left ventricular hypertrophy.

## CONCLUSION

The  $\beta_1$ -receptor blockade reduces resting blood flow and increases the myocardial flow reserve. This finding may have important implications in the clinical setting. First,  $\beta_1$ -receptor blockers do not need to be discontinued before pharmacological stress testing with dipyridamole. The current findings suggest that  $\beta_1$ -receptor antagonists do not blunt the pharmacological effects of dipyridamole. The reduction in resting blood flow and improved vasodilatory capacity may raise the threshold for ischemic events in patients with coronary artery disease (2,3).

## ACKNOWLEDGMENTS

We thank Ron Sumida, Larry Pang, Der-Jenn Liu and Francine Aguilar for their technical assistance, Diane Martin for the illustrations and Eileen Rosenfeld for her skillful assistance in preparing this manuscript. The Laboratory of Structural Biology and Molecular Medicine is operated for the U.S. Department of Energy by the University of California, Los Angeles, CA under contract no. DE-FC03-87ER60615. This work was supported in part by the Director of the Office of Energy Research, Office of Health and Environmental Research, Washington, D.C., by research grant nos. HL 29845 and HL 33177, National Institutes of Health, Bethesda, MD and by an Investigative Group Award by the Greater Los Angeles Affiliate of the American Heart Association, Los Angeles, CA. Dr. Morten Böttcher is the recipient of an educational grant from the Danish Heart Association and the Danish Research Council.

## REFERENCES

1. Parrat J, Grayson J. Myocardial vascular reactivity after beta-adrenergic blockade. *Lancet* 1996;1:338-340.
2. Frishman W. Multifactorial actions of beta adrenergic blocking drugs in ischemic heart disease. *Circulation* 1983;67:(suppl 1):111-118.
3. Braunwald E, Muller J, Kloner R, et al. Role of beta adrenergic blockade in the therapy of patients with myocardial infarction. *Am J Med* 1983;74:113-123.
4. Marzilli M, Goldstein S, Sabbah H, et al. Modulating effect of regional myocardial performance on local myocardial perfusion in the dog. *Circ Res* 1979;45:634-643.
5. McGinn A, White C, Wilson R. Interstudy variability of coronary flow reserve: influence of heart rate, arterial pressure and ventricular preload. *Circulation* 1990; 1319-1330.
6. Schelbert HR, Phelps ME, Huang SC, et al. Nitrogen-13-ammonia as an indicator of myocardial blood flow. *Circulation* 1981;63:1259-1272.
7. Krivokapich J, Smith GT, Huang SC, et al. Nitrogen-13-ammonia myocardial imaging at rest and with exercise in normal volunteers: quantification of absolute myocardial perfusion with dynamic PET. *Circulation* 1989;80:1328-1337.
8. Kuhle W, Porenta G, Huang S-C, et al. Quantification of regional myocardial blood flow using  $^{13}\text{N}$ -ammonia and reoriented dynamic positron emission tomographic imaging. *Circulation* 1992;86:1004-1017.
9. Hutchins G, Schwaiger M, Rosenspire K, et al. Noninvasive quantification of regional blood flow in the human heart using  $^{13}\text{N}$ -ammonia and dynamic PET imaging. *J Am Coll Cardiol* 1990;15:1032-42.
10. Diamond G, Forrester J. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979;300:1350-1358.
11. Smits P, Lenders JW, Thien T. Caffeine and theophylline attenuate adenosine induced vasodilation in humans. *Clin Pharmacol Ther* 1990;48:410-418.
12. Böttcher M, Czernin J, Sun K, et al. Effect of caffeine on myocardial blood flow at rest and during pharmacological vasodilation. *J Nucl Med* 1995;36:2016-2021.
13. Spinks TJ, Guzzardi R, Bellina CR. Performance characteristics of a whole-body PET. *J Nucl Med* 1988;29:1833-1841.
14. Porenta G, Kuhle W, Czernin J, et al. Semiquantitative assessment of myocardial viability and perfusion utilizing polar map displays of cardiac PET images. *J Nucl Med* 1992;33:1623-1631.
15. Kuhle W, Porenta G, Huang S-C, et al. Issues in the quantitation of reoriented cardiac PET images. *J Nucl Med* 1992;33:1235-1242.
16. Czernin J, Sun K, Brunken R, et al. Effect of acute and chronic smoking on myocardial blood flow and flow reserve. *Circulation* 1995;91:2891-2897.
17. Czernin J, Auerbach M, Sun K, et al. Effects of modified pharmacologic stress approaches on hyperemic myocardial blood flow. *J Nucl Med* 1995;36:575-580.
18. Czernin J, Barnard R, Krivokapich J, et al. Effect of short-term cardiovascular conditioning and low fat diet on myocardial blood flow and flow reserve. *Circulation* 1995;92:197-204.
19. Czernin J, Müller P, Chan S, et al. Influence of age and hemodynamics on myocardial blood flow and flow reserve. *Circulation* 1993;88:62-69.
20. Weinberg IN, Huang SC, Hoffman EJ, et al. Validation of PET-acquired functions for cardiac studies. *J Nucl Med* 1988;29:241-247.
21. Gambhir SS, Schwaiger M, Huang SC, et al. Simple noninvasive quantification method for measuring myocardial glucose utilization in humans employing PET and fluorine-18-deoxyglucose. *J Nucl Med* 1989;30:359-366.
22. Krivokapich J, Stevenson L, Kobashigawa J, et al. Quantification of absolute myocardial perfusion at rest and during exercise with PET after human cardiac transplantation. *J Am Coll Cardiol* 1991;18:512-517.
23. Braunwald E. Control of myocardial oxygen consumption: physiologic and clinical considerations. *Am J Cardiol* 1971;27:416-422.
24. Ross J, Sonnenblick E, Kaiser G, et al. Electroaugmentation of ventricular performance and oxygen consumption by repetitive application of paired electrical stimuli. *Circ Res* 1965;16:332-342.
25. Graham T, Covell J, Sonnenblick E, et al. Control of myocardial oxygen consumption: relative influence of contractile state and tension development. *J Clin Invest* 1968;47: 332-343.
26. Holmberg S, Serzysko W, Varnauskas E. Coronary circulation during heavy exercise in control subjects and patients with coronary heart disease. *Acta Med Scand* 1971;190:465-480.
27. Czernin J, Porenta G, Brunken R, et al. Regional blood flow, oxidative metabolism and glucose utilization in patients with recent myocardial infarction. *Circulation* 1993;88: 884-895.
28. Grandin C, Wijns W, Melin J, et al. Prediction of functional improvement with PET in patients recovering from acute anterior ischemia. *J Nucl Med* 1995;36:1543-1552.
29. Sievert H, Frey G, Schrader R, et al. Influence of carvedilol and propranolol on coronary blood flow. *Eur J Clin Pharmacol* 1990;38:(suppl):S122-124.
30. Hoffman E. Maximal coronary flow and the concept of coronary vascular reserve. *Circulation* 1984;70:153-165.
31. Bache R, Cobb F. Effect of maximal coronary vasodilation on transmural myocardial perfusion during tachycardia in the awake dog. *Circ Res* 1977;41:648-653.
32. Müller P, Czernin J, Choi Y, et al. Effect of exercise supplementation during adenosine infusion on hyperemic blood flow and flow reserve. *Am Heart J* 1994;128:52-60.