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Attenuation of Coronary Vascular Resistance by Selective Alpha$_1$-Adrenergic Blockade in Patients With Coronary Artery Disease

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Alpha-adrenergic–mediated coronary vasoconstriction during stress such as cold pressor testing may contribute to myocardial ischemia by increasing coronary vascular resistance in patients with severe coronary artery disease. Nonselective alpha-receptor blockade with phentolamine abolishes both the peripheral and coronary vasoconstriction during cold pressor testing, but causes reflex tachycardia and increased inotropy. To determine the role of selective alpha$_1$-receptor blockade, the changes in coronary vascular resistance during cold pressor testing were measured in 18 patients with coronary artery disease before and after intravenous administration of 100 mg of trimazosin. Cold pressor testing was performed at a constant paced subanginal heart rate of 95 ± 5 beats/min (± 1 SD). Before trimazosin, cold pressor testing increased mean arterial pressure by 9 ± 4% (102 ± 14 to 111 ± 14 mm Hg, $p < 0.001$) with no change in coronary sinus blood flow, but significantly increased coronary vascular resistance by 15 ± 19% (1.02 ± 0.46 to 1.15 ± 0.57 units, $p < 0.05$). Five minutes after trimazosin, cold pressor testing increased mean arterial pressure by 6 ± 5% ($p < 0.001$) with a marked attenuation of the increase in coronary vascular resistance (6 ± 11%, p = NS), which was significantly less than before trimazosin ($p < 0.02$). Trimazosin did not increase plasma norepinephrine concentration at rest, suggesting that in the dosage used trimazosin caused selective alpha$_1$-receptor blockade.

These data suggest that although the hypertensive response to cold pressor testing is somewhat blunted by selective alpha$_1$-adrenoceptor blockade, the reflex coronary vasoconstriction during adrenergic stimulation in some patients with coronary artery disease can be significantly attenuated. Use of agents that block alpha$_2$-adrenoceptors has been clinically unsatisfactory because of the adverse myocardial effects of increased norepinephrine release. Selective alpha$_1$-receptor blockade may have an additional advantage over nonselective alpha-adrenergic blockade in that the release of norepinephrine is also attenuated, thus potentially producing less augmentation of heart rate and myocardial oxygen demand.

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Alpha-adrenergic–mediated coronary vasoconstriction during stress such as cold pressor testing may contribute to myocardial ischemia in patients with coronary artery disease (1,2). Extensive investigations (3–9) have documented the role of alpha-adrenergic vasoconstriction on coronary blood flow. Increased alpha vasoconstrictor tone has been implicated in the exacerbation of coronary spasm after subcutaneous administration of epinephrine in patients receiving propranolol (10). Beta-receptor blockade with propranolol has been reported to intensify the duration of myocardial ischemia and ventricular ectopic activity in patients with vasospastic angina pectoris, presumably through inhibition of beta$_2$-receptor–mediated coronary vasodilation, resulting in unopposed alpha-adrenergic–mediated vasoconstriction (11). Recently, potentiation of alpha vasoconstrictor activity has been demonstrated after acute beta-adrenergic blockade during cold pressor testing (12).

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Clinical application of nonselective alpha-adrenergic antagonists, such as phentolamine, as vasodilators has been unsatisfactory because of the increased circulating norepinephrine after blockade of alpha$_2$-receptors, increasing the heart rate, contractility and myocardial oxygen consumption (13). We speculated that selective alpha$_1$-receptor blockade might inhibit coronary vasoconstriction without inducing the associated adverse myocardial effects of nonselective alpha-receptor blockade. Accordingly, the purpose of this investigation was to determine whether selective alpha$_1$-receptor blockade with trimazosin could attenuate the inappropriate reflex increase in coronary vascular resistance during the adrenergic stimulation of cold pressor testing.

Methods

Study patients. Eighteen patients undergoing diagnostic cardiac catheterization for chest pain were studied. Patients were excluded who had unstable angina, coexistent valvular heart disease, myocardial infarction within 6 weeks of study, severe left ventricular dysfunction, greater than 50% left main coronary artery stenosis, concomitant treatment with calcium channel blocking drugs or nonsteroidal anti-inflammatory drugs or contraindication to the use of alpha$_1$-adrenergic blocking agents.

Study protocol. The investigational protocol and consent form were approved by the Human Subjects Committee of the Brigham and Women's Hospital. After written informed consent was obtained, treatment with beta-adrenergic blocking agents was withheld in all patients at least 18 hours, and treatment with long-acting nitrate preparations at least 6 hours before catheterization. As part of the diagnostic protocol, nitroglycerin, 0.4 mg sublingually, and atropine, 0.4 mg intravenously, were given before coronary angiography in all patients.

To minimize the metabolic and vasodilator effects of radiographic contrast material after the completion of left ventriculography and coronary angiography (14), at least 15 minutes elapsed before an 8F coronary sinus thermodilution pacing catheter (Wilton Webster Laboratories) was positioned in the coronary sinus by way of an antecubital vein for the study protocol. Fluoroscopy confirmed proper location and the stable coronary sinus catheter position during the study. Mean and phasic arterial pressures were measured with a femoral artery catheter. Arterial and coronary sinus blood oxygen content was measured using a fuel cell method (Lex-O_2-Con, Lexington Instruments). Arterial and coronary sinus blood for lactate concentration was determined by standard enzymatic assay. All pressures, coronary flow signals and electrocardiogram were recorded on a multichannel optical strip chart recording system (Electronics for Medicine).

Cold pressure testing. Ten minutes after placement of the coronary sinus catheter, measurements of phasic and mean arterial pressure, heart rate, coronary sinus blood flow and arterial and coronary sinus oxygen and lactate contents were made at rest and during cold pressor testing, before and 5 minutes after intravenous administration of 100 mg of trimazosin. To evaluate the effects of trimazosin after a longer equilibration period, a third cold pressor test was performed in eight patients 30 minutes after trimazosin administration. Cold pressor testing was performed as in previous studies (1,12,15). In brief, cold pressor testing measurements were made during coronary sinus pacing at a constant subanginal rate (95 ± 5 beats/min) to eliminate the influence of heart rate changes on coronary sinus blood flow, and at the identical paced heart rate during immersion of the hand and forearm in ice water for 90 seconds. At least a 5 minute equilibration period allowed hemodynamic measurements to return to baseline values between cold pressor testing.

Plasma norepinephrine. Femoral artery blood samples for plasma norepinephrine determinations were collected (3 ml into reduced glutathione) before and 5 (18 patients) and 30 (8 patients) minutes after administration of trimazosin at rest. Plasma norepinephrine was determined by radioenzyme assay as previously described (16). Blood samples were not obtained during cold pressor testing because this stimulus is known to produce significant increases in systemic and transmyocardial catecholamine concentrations (17,18). The normal plasma norepinephrine concentration (± 1 standard deviation) in our laboratory is 213 ± 30 pg/ml.

Data analysis. Coronary sinus blood flow was calculated from simultaneously recorded temperature signals by the method of Ganz et al. (19). Heart rate was calculated from the electrocardiogram. Coronary vascular resistance was calculated as the quotient of mean arterial pressure and coronary sinus blood flow. Arterial-coronary sinus oxygen content difference was expressed in milliliters of oxygen per deciliter of blood.

Statistical analysis. The effects of trimazosin before and after cold pressor testing were assessed by analysis of variance. Whenever such analysis indicated a significant contribution of a particular variable to total sample variability, subsequent comparisons between the individual groups were performed using the appropriate paired or nonpaired Student's two-tailed *t* test. Results are expressed as mean ± standard deviation and a probability (p) value of less than 0.05 was regarded as statistically significant.

Results

Clinical data (Table 1). Seven of the 18 patients were not receiving beta-receptor blocking drugs before study. Two patients were receiving metoprolol before study; seven patients were receiving propranolol, one patient was receiving nadolol and one was receiving timolol. Beta-recep-

Table 1. Clinical and Hemodynamic Data in 18 Patients

Case	Age (yr) & Sex	Beta-Blocking Agent* (mg/24 h)	RCA (%)	LAD (%)	LCx (%)	RAP (mm Hg)	PCW (mm Hg)	LVEF (%)	LVWM
1	36M	0	100	40	100	6	7	47	ApH,IA
2	46M	80,n	60	100	90	5	9	81	N
3	69F	80	0	99	0	11	11	70	ApH
4	55M	480	100	70	90	8	14	64	IH
5	63M	100,m	40	70	0	3	4	68	N
6	66M	0	90	90	80	4	7	55	AnH
7	57M	0	100	100	75	3	7	66	AnA,ID
8	55F	160	95	0	0	7	13	71	N
9	58M	480	100	99	50	5	10	76	N
10	54M	0	100	60	100	4	5	47	IA,AnH
11	59M	0	0	85	100	2	9	69	IH
12	54M	0	100	60	95	3	6	76	IH
13	63M	100,m	100	95	0	3	9	61	ID
14	43M	0	50	50	70	9	13	60	IH
15	60M	120	0	0	90	5	5	75	AnH
16	71M	40	0	50	70	2	9	64	N
17	59M	80	70	90	0	7	10	67	N
18	67M	20,t	90	60	100	2	9	45	AnH,IH
Mean ± SD	58 ± 9					5 ± 3	9 ± 3	65 ± 11	

*The beta-adrenergic blocking agent is propranolol unless marked with subscript: m = metoprolol, n = nadolol, t = timolol. A = akinesia; An = anterior; Ap = apical; D = dyskinesia; F = female; H = hypokinesia; I = inferior; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery stenosis; LVEF = left ventricular ejection fraction; LVWM = left ventricular wall motion abnormality; M = male; N = normal; PCW = pulmonary capillary wedge pressure; RAP = right atrial pressure; RCA = right coronary artery.

tor blockade was withheld at least 18 hours in all patients. Patient 2, in whom nadolol was discontinued 18 hours before study, had similar cold pressor responses as observed in the group data and was included in the analysis. No patient experienced angina during the initial or subsequent cold pressor testing. There was no difference in rest or cold pressor testing response between patients with typical or atypical angina pectoris.

Rest hemodynamic response to trimazosin (Table 2). At rest 5 minutes after trimazosin administration, mean arterial pressure decreased from 98 ± 10 to 93 ± 7 mm Hg ($p < 0.01$ versus control) and 30 minutes after trimazosin to 88 ± 6 mm Hg ($p < 0.01$ versus control). There was no statistically significant increase in coronary sinus blood flow at rest, coronary vascular resistance, serum norepinephrine concentration or heart rate after the administration of trimazosin.

Cold pressor hemodynamic responses to trimazosin (Table 3). During cold pressor testing before trimazosin administration, mean arterial pressure increased by 9% from 102 ± 14 to 111 ± 14 mm Hg ($p < 0.001$), with no change in coronary sinus blood flow (114 ± 40 to 111 ± 40 ml/min, p = NS) and a 14% increase in coronary vascular resistance from 1.02 ± 0.46 to 1.16 ± 0.57 units ($p < 0.02$).

Five minutes after trimazosin administration, cold pressor testing increased mean arterial pressure by 6% (95 ± 9 to 101 ± 10 mm Hg, $p < 0.001$) with no change in coronary sinus blood flow (110 ± 49 to 112 ± 53 ml/min, p = NS) or coronary vascular resistance (1.05 ± 0.53 to 1.11 ± 0.62 units, p = NS). The cold pressor testing response was similar 30 minutes after trimazosin. Cold pressor testing 30 minutes after trimazosin administration in eight patients increased mean arterial pressure by 4% from 92 ± 9 to 96 ± 8 mm Hg ($p < 0.01$) with no increase in

Table 2. Mean Rest Hemodynamics and Norepinephrine Concentration Before and After Trimazosin Administration in 18 Patients

	HR (beats/min)	MAP (mm Hg)	CSBF (ml/min)	CVR (units)	NOR (pg/ml)
Control	71 ± 12	98 ± 10	105 ± 34	1.01 ± 0.34	240 ± 40
T5	74 ± 12	93 ± 9*	108 ± 46	0.93 ± 0.28	251 ± 35
T30	76 ± 12	88 ± 6*	110 ± 35	0.86 ± 0.26	256 ± 50

*$p < 0.01$ versus control. Values represent mean ± standard deviation. CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; HR = heart rate; MAP = mean arterial pressure; NOR = serum norepinephrine concentration; T5 = 5 minutes after trimazosin; T30 = 30 minutes after trimazosin.

Table 3. Hemodynamic Response During Cold Pressor Testing Before and After Trimazosin Administration in 18 Patients

	ΔBP (%)			ΔCSF (ml/min)			ΔCVR (units)			ΔCVR (%)		
Case	C	T5	T30	C	T5	T30	C	T5	T30	C	T5	T30
1	17	7	–	3	−2	–	0.09	0.04	–	15	8	–
2	3	3	–	−8	−1	–	0.10	0.05	–	12	5	–
3	13	6	–	−7	−1	–	0.77	0.68	–	33	29	–
4	10	3	–	−28	−19	–	0.57	0.32	–	54	31	–
5	7	15	–	−4	17	–	0.14	−0.15	–	12	−11	–
6	13	6	–	−3	5	–	0.12	0.02	–	25	2	–
7	8	4	–	4	4	–	0.05	−0.06	–	4	4	–
8	4	6	–	−5	−5	–	−0.20	−0.01	–	−12	0	–
9	10	19	–	13	6	–	0.0	0.09	–	0	14	–
10	7	4	–	−42	−3	–	0.34	0.07	–	50	7	–
11	6	2	3	5	0	0	0.02	0.01	0.03	2	1	4
12	12	10	15	9	7	42	−0.02	0.03	−0.10	−3	5	−16
13	9	7	2	11	16	6	−0.06	−0.15	−0.05	−4	−11	−4
14	12	11	9	0	27	23	0.07	0.0	−0.01	12	0	−2
15	11	3	1	13	0	11	−0.03	0.02	−0.07	−3	2	−6
16	2	5	6	−44	−7	−21	0.33	0.07	0.13	43	10	22
17	6	2	0	−7	−6	11	0.13	0.05	−0.07	14	7	−9
18	9	1	1	0	6	0	0.05	−0.02	0.01	8	−3	1
Mean	9	6	5	−5	2	9	0.14	0.06	−0.02	15	6	−1
± SD	4	5	5	17	10	18	0.23	0.18	0.07	19	11	11
p Value	NS			0.05			0.01			0.02		
	0.05			NS			NS			0.05		

Δ = change during cold pressor testing; BP = mean arterial pressure; C = control; CSF = coronary sinus blood flow; CVR = coronary vascular resistance; T5 = 5 minutes after trimazosin; T30 = 30 minutes after trimazosin.

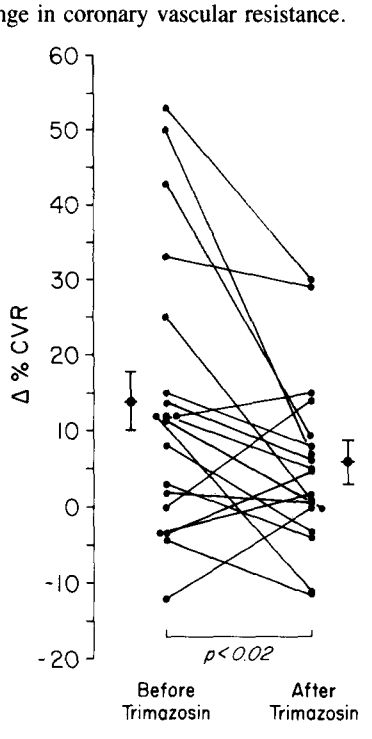
either coronary sinus blood flow (129 ± 34 to 138 ± 37 ml/min, p = NS) or coronary vascular resistance (0.75 ± 0.19 to 0.74 ± 0.18 units, p = NS).

Because of the heterogeneous nature of coronary artery disease, there is a large variability among cold pressor testing responses. Figure 1 shows the individual patient responses during cold pressor testing before and 5 minutes after trimazosin administration. The increase in coronary vascular resistance during cold pressor testing was attenuated from 14 ± 4 to 6 ± 3% after trimazosin administration ($p < 0.02$). Figure 2 summarizes the changes during cold pressor testing in mean arterial pressure and coronary sinus flow and resistance before and after trimazosin. No changes in arterial-coronary sinus oxygen difference (0.02 ± 0.6 versus −0.15 ± 0.7 ml/dl, p = NS) or lactate extraction (0.11 ± 0.20 versus 0.50 ± 0.42 mEq/liters, p = NS) during cold pressor testing were found before or after trimazosin.

Discussion

This study suggests that selective alpha$_1$-adrenergic blockade with trimazosin attenuates the reflex coronary vasoconstriction during the adrenergic stimulus of cold pressor testing in patients with coronary artery disease. Our data are in agreement with experimental and clinical studies (20,21) reporting a reduction in coronary vascular resistance after alpha$_1$-receptor blockade, and may be best interpreted by considering studies relating alpha-adrenoceptor regulation of coronary blood flow and vasoreactivity.

Figure 1. Individual patient responses during cold pressor testing before and *5 minutes* after trimazosin administration. Δ% CVR = percent change in coronary vascular resistance.



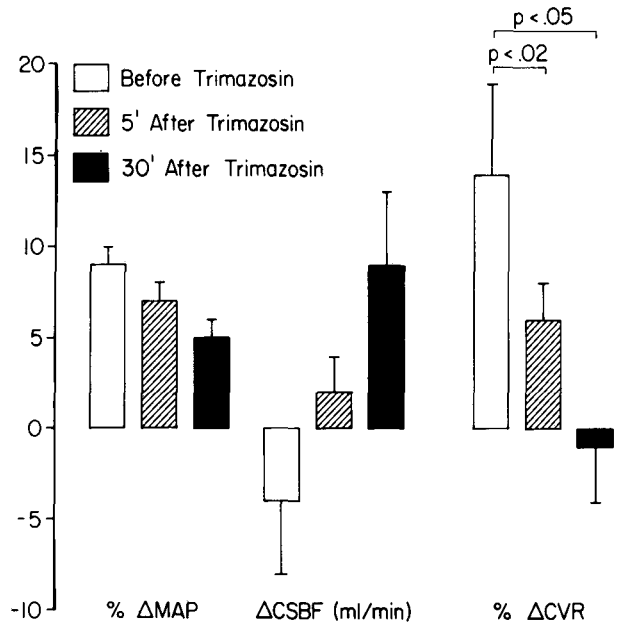


Figure 2. Hemodynamic changes (Δ) during cold pressor testing. CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; MAP = mean arterial pressure. 5′ and 30′ = 5 and 30 minutes, respectively.

Alpha-adrenergic receptors and coronary vascular resistance. Alpha-adrenergic tone appears to have a significant role in regulating coronary blood flow (3,22–25). The net result of alpha-adrenoceptor stimulation depends on the interaction of alpha-receptor subtypes. Activation of alpha$_1$-receptors causes vasoconstriction, while the occupation of the alpha$_2$-receptors by norepinephrine inhibits further release of norepinephrine from postganglionic sympathetic nerve terminals (26,27). Alpha-adrenergically mediated changes in coronary vascular resistance are capable of competing with and overcoming opposing metabolic vasodilator influences (6). However, extrapolation of data from numerous animal studies on the role of alpha-receptors to human beings is difficult. The in vivo effects of alpha-receptor activation and blockade on the atherosclerotic human coronary vasculature are poorly defined. A pathophysiologic role for alpha-adrenergic–mediated vasoconstriction is implicated in patients during cold pressor stress (1,12), coronary vasospasm (10,11), exercise (26,28) and unstable angina (29). However, nonselective alpha-adrenergic blocking agents have not been advocated in patients with coronary artery disease because of increased myocardial oxygen consumption due to increased inotropy and reflex tachycardia (13). In our patients, selective alpha$_1$-receptor blockade reduced mean arterial pressure approximately 10% without significant increases in heart rate, arterial norepinephrine concentration or heart rate-pressure product (as an index of myocardial oxygen demand).

Mechanisms. The mechanism responsible for the abnormal vasoconstrictor response during adrenergic stimulation in patients with coronary artery disease is unclear. Alpha-mediated vasoconstriction may involve large epicardial vessels, precapillary arterioles or intramyocardial capillaries to different degrees depending on regional differences in alpha-adrenoceptor concentration, distribution and sensitivity (22,24,30–32). Autoregulation cannot be discounted as a vasodilator mechanism when constant coronary blood flow is maintained despite reduced arterial pressure. We do not believe that metabolic autoregulation of coronary blood flow alone was responsible for the changes in coronary resistance observed during cold pressor testing after trimazosin administration. Trimazosin administration was not associated with a significant decrease in the heart rate-blood pressure product or a narrowing of the arterial-coronary sinus oxygen difference during cold pressor testing to suggest reduced metabolic myocardial demand. It is possible that the lower initial arterial pressure with a relative decrease in myocardial oxygen demand alters the response of the coronary bed to the cold pressor vasoconstrictor stimulus. There was no correlation between initial mean arterial pressure and change in coronary vascular resistance during cold pressor testing. It also appears unlikely that trimazosin should alter coronary vascular resistance by any direct effect on vascular smooth muscle (33).

Trimazosin appears to attenuate vascular resistance components in both the coronary circulation and systemic arterial bed. After trimazosin administration during cold pressor testing, there is a somewhat greater reduction of coronary vascular resistance compared with the systemic pressure response. The reason for this differential effect is unclear, but it may be due to differences in the distribution, number and predominant alpha-adrenoceptor subtype in the coronary compared with the peripheral vasculature (24,34,35).

Selection of alpha$_1$-receptor blocking agent. Trimazosin, unlike prazosin, can be administered intravenously and appears to be a more potent coronary vasodilator. Studies in the conscious dog (20,21,36–39) comparing nonselective alpha-receptor blockade with phentolamine with prazosin and trimazosin showed that all three agents reduced systemic arterial pressure, but coronary resistance decreased significantly more with trimazosin than with either prazosin or phentolamine. Specific doses of the alpha$_1$-receptor blocking drug, trimazosin, in human beings have been empirically determined. Data from our preliminary studies and those of others (36,38) indicated that a modest reduction of mean arterial pressure without reflex changes in heart rate occurs with the doses used for this study. No significant side effects of tachycardia or hypotension were seen with 100 mg of intravenous trimazosin. Because alpha$_2$-receptor stimulation inhibits release of norepinephrine into the neural synapse during sympathetic impulse transmission, a four- to fivefold increase in circulating norepinephrine (13,26) would be expected if alpha$_2$-receptor blockade occurred. However, in this study, trimazosin administration did not

elicit an increase in arterial norepinephrine concentration, excluding significant presynaptic blocking action.

Study limitations. Certain limitations of ths study should be noted. Cold pressor testing is an artificial stimulus and may be difficult to extrapolate to clinical correlations; however, it consistently increases coronary vascular resistance in patients with significant coronary artery disease and provides a reproducible model to assess changes in human coronary resistance. Variable coronary resistance responses have been observed (40) in patients with lesser degrees of coronary artery disease during cold pressor testing. The cold pressor induced-coronary vascular resistance responses of the five patients with minimal and single vessel coronary artery disease were not significantly different from the group data.

One major limitation of this study was the evaluation of only global coronary vascular resistance responses to trimazosin. Regional coronary vascular resistance responses to alpha$_1$-receptor blockade may differ from total coronary vascular resistance depending on several factors, such as extent of coronary disease, degree of collateral blood flow and regional autoregulatory capacity. In our patients, trimazosin may have blunted vasoconstriction in diseased arterial segments to a different degree than in normal segments with the net result of a small increase in global coronary sinus flow and a decrease in coronary vascular resistance. Further investigation into regional changes in coronary resistance after alpha$_1$-receptor blockade is warranted.

Thermodilution coronary sinus blood flow measurements can be affected by small changes in catheter position. Relative changes in flow and resistance have therefore been used to indicate directional effects and the interpretation of these data need not depend on the absolute magnitude of the changes in coronary vascular resistance. Studies in which right atrial reflux, flow signal artifacts or extrasystoles appeared during measurements were excluded from analysis (41).

Concurrent effects of other pharmacologic agents complicate the interpretation of changes in coronary resistance. Resolution of preexisting beta-adrenergic blockade after 18 hours may be incomplete, especially in patients taking long-acting beta-receptor blocking drugs (42,43). However, any residual beta-receptor blockade would be expected to augment the changes in coronary vascular resistance during cold pressor testing (12). Thus, changes in coronary vascular resistance after administration of trimazosin would be more significant than in the complete absence of beta-receptor blockade. Although reported to abolish coronary vasospasm (44), atropine did not alter coronary vasomotor responses during cold pressor testing (12) and, in this study, was a constant factor for all patients.

Clinical significance. Although selective alpha$_1$-receptor blockade with trimazosin can attenuate the increase in coronary vascular resistance during adrenergic stimulation, the clinical significance of this observation for patients with coronary artery disease has yet to be determined. Indeed, alpha$_1$-receptor blockade with prazosin has no obvious beneficial effects in patients with variant angina (45,46) and in one study (47), has been reported to exacerbate classic angina pectoris. In a subset of patients with coronary artery disease in whom a vasodilator is indicated, selective alpha$_1$-receptor blockade may have a potential advantage over other vasodilators, such as hydralazine or nonselective alpha-receptor blocking drugs. Trimazosin, in addition to attenuation of coronary vascular resistance, appears to result in a lesser degree of peripheral norepinephrine release and thus, potentially, less augmentation of heart rate and factors increasing myocardial oxygen demand.

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