

Mechanism of bronchoconstriction due to beta adrenergic blockade

Studies with practolol, propranolol, and atropine

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Partial beta adrenergic blockade has been proposed as a basic defect in asthma. Six chronic asthmatic subjects were studied in the supine position with measurements of expiratory flow, cardiac output, blood pressure, heart rate, and arterial blood gases. Propranolol, in doses varying from 10 to 20 mg. intravenously, resulted in a 20 per cent decrease of FEV₁ in 4 of these patients, while reductions of Pa_o, and cardiac index were not significant. In a fifth patient, severe respiratory distress developed following 3 mg. of propranolol. Aerosol atropine, delivered in a concentration of 2.5 mg. per milliliter, resulted in a marked improvement in FEV₁ and VC in 4 of these patients and inhibited a bronchoconstrictive response to subsequent intravenous propranolol. This suggests that propranolol-induced bronchoconstriction in asthmatic subjects results from unopposed intrinsic parasympathomimetic activity. Practolol, a recently developed beta adrenergic antagonist, was administered in doses of 25 to 50 mg. intravenously to all 6 asthmatic subjects without reduction of FEV₁ or VC. These observations indicate that cardiovascular and pulmonary beta adrenergic receptors are not identical and are susceptible to selective blockade.

The hypothesis that asthma is due to functional imbalance of the autonomic nervous system was proposed by Eppinger and Hess¹ in 1917 when they presented their concept of vagotonia and suggested that asthma might be due to excessive cholinergic activity. An important advance in the study of the autonomic nervous system was introduced by Ahlquist² in 1948 when he proposed that the variable actions of epinephrine and other sympathomimetic drugs could be accounted for if two sets of receptors, alpha and beta, were present in or near end organs affected by these substances. A series of investigations in animals has led Szentivanyi and others³⁻⁴ to the hypothesis that partial beta adrenergic blockade is a cause of bronchial hypersensitivity in human beings. Normal mice sensitized with an injection of *Bordetella pertussis* organisms demonstrate a 30- to 300-fold increased sensitivity to histamine and a 20- to 50-fold increased sensitivity to serotonin. In nonimmunized mice treated with dichloroisoproterenol, a beta adrenergic blocking agent, a similar hypersensitivity to the effects of histamine and serotonin developed.

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The beta adrenergic theory of human bronchial asthma has been extensively reviewed by both Szentivanyi⁵ and Reed.⁶ The beta receptor theory states that excessive irritability of the bronchial tree is the fundamental abnormality of asthma, and that the cause of the excessive irritability is a diminished responsiveness of the beta adrenergic receptors of the bronchial glands, smooth muscle, and mucosal blood vessels. This has been proposed as an explanation for the triggering of bronchoconstriction by a large variety of nonallergic stimuli such as infection, psychic factors, inhalation of cold air, nonantigenic dusts, and fumes.

This report presents studies in asthmatic patients designed to define the mechanism of bronchoconstriction following parenteral administration of beta adrenergic antagonists, with particular reference to the role of unopposed intrinsic parasympathomimetic activity.

MATERIALS AND METHODS

Six chronic asthmatic subjects were recruited from an allergy clinic population. Four men and two women, ages 35 to 59, were studied with informed consent after a 12 hour fast, and they were off medications for at least 12 hours prior to the study. At the time of the study, 3 patients were on maintenance prednisone therapy, 10 mg. daily. Patients were studied supine. Arterial pressure was monitored continuously by an indwelling arterial cannula inserted 20 minutes prior to initiation of the control period measurements. A 24 inch polyethylene float catheter was advanced to the superior vena cava for radioisotope injection and for drug infusion. Expiratory flow measurements, including forced expiratory volume in one second (FEV₁), vital capacity (VC), and per cent FEV₁/VC, were made with a standard pneumotachometer and appropriate integrating circuitry as reported previously from this laboratory.⁷ Prior to each study standardization with a Collins spirometer was performed.

Each subject was studied on two occasions separated by at least one week. The two protocols were similar, except that the beta adrenergic blocking drug used in the first study was practolol*; in the paired second study, propranolol was infused.

After 20 minutes of acclimatization to the study conditions, paired cardiac output measurements were made. Cardiac output was estimated according to the method of Gorten and Stauffer⁸ by external monitoring of the cardiac transit of iodine-131-labeled human serum albumin (¹³¹IHSA). Cardiac index (cardiac output per square meter of body surface area) was used in order to permit comparison of results in subjects of varying size. Arterial samples were drawn for blood gas analysis. FEV₁ was measured in triplicate and the highest measurement selected.

Ten-minute drug infusions with a pump were instituted via the caval catheter. In the first study, 25 mg. of practolol (4-[2-hydroxy-3-isopropylaminopropoxy] acetoniide) was administered to the initial 2 patients and 50 mg. to the remaining 4. During the second period 10 mg. of propranolol was delivered to the initial 2 patients and 20 mg. to Patients 4 and 5. In the third asthmatic patient the infusion was discontinued after 3 mg. led to severe respiratory obstruction, while the sixth patient was not studied.

In the study with propranolol, a second control period of 10 minutes was followed by a 10 minute period of aerosol atropine administration, 2.5 mg. per milliliter via a De Vilbiss nebulizer at 5 L. air flow per minute. Although 2 ml. of this solution was nebulized, the dose retained by the patient remained unknown. Following this, propranolol was reinfused over a 10 minute period at the same dose as before atropine. Between the seventh and tenth minute of each of these periods, hemodynamic, blood gas, and expira-

*AY21,011, kindly supplied by Dr. A. Sahagian-Edwards and Dr. R. O. Davies, Ayerst Inc., 685 Third Avenue, New York, N. Y. 10017.

tory flow measurements were repeated as in prior periods, with the exception that only one cardiac output measurement was made.

Tests of significance for differences between measurements for the group of subjects were carried out in all instances by the paired Student's *t* test in which each study period measurement is compared with the control period measurement for the same subject.

RESULTS

Table I shows the individual responses and the group means of pulmonary and hemodynamic changes with propranolol infusions before and after administration of atropine aerosol in 4 asthmatic patients and with propranolol alone in a fifth patient. The last two columns in Table I show the comparable results with practolol in the same 5 subjects and an additional patient studied on a different day.

The control period FEV₁ was markedly decreased to an average of 31 per cent of predicted normal (range 19 to 52 per cent), indicative of the asthmatic state. PaO₂ was reduced only slightly, and hemodynamic measurements were normal.

Propranolol study

Propranolol resulted in further reduction in flow rates. FEV₁ was the most sensitive index of increased airway resistance, falling by 20 ± 7 per cent ($p < 0.01$) from control levels. Nonsignificant reductions in PaO₂ (-10 ± 12 per cent, $p < 0.1$) and in cardiac index (-10 ± 24 per cent, $p < 0.25$) were observed. Peripheral resistance was increased in proportion to the fall in cardiac index. Arterial pressure and heart rate did not change significantly. Subject No. 3 suffered severe respiratory distress after infusion of 3 mg. of propranolol and required intubation for relief; no subsequent measurements could be made. Therefore the mean values measured during the propranolol infusion do not reflect the severe physiological decompensation developed by the subject most sensitive to propranolol.

Atropine by aerosol resulted in a marked improvement in FEV₁ and VC. FEV₁ improved to 36 ± 8 per cent ($p < 0.01$); VC improved to $+31 \pm 18$ per cent ($p < 0.01$). In each instance the measurements indicated not only reversal of the propranolol-related bronchoconstriction but also varying degrees of improvement toward the predicted levels, as shown in a typical case in Fig. 1. There were no significant hemodynamic changes or evidence of hemodynamic vagal blockade from bronchial administration of atropine at this dose level.

Subsequent infusion of propranolol indicated that atropine reversal of propranolol-induced bronchoconstriction was effective, as expiratory flow measurements, FEV₁, and VC did not fall significantly from the improved levels reached after aerosol atropine administration.

Practolol study

Practolol infusion did not decrease the FEV₁, VC, and FEV₁/VC per cent in the 6 patients studied. The divergent FEV₁ responses to propranolol and practolol in 5 asthmatic patients is presented in Fig. 2.

TABLE I. Respiratory and hemodynamic measurements in asthmatic subjects

	Subjects*	Propranolol study					Practolol study	
		Control	Predicted	% Change from initial control			Control	% Change from control
				Propranolol	Atropine	Propranolol after atropine		
FEV ₁ (ml.)	1	652	3,580	-18 (10 mg.)	+31	+31	725	+ 7 (25 mg.)
	2	2,036	3,880	-18 (10 mg.)	+31	+35	2,119	+43 (25 mg.)
	3	345	2,500	Respiratory distress (3 mg.)			345	- 1 (50 mg.)
	4	1,125	2,700	-13 (20 mg.)	+33	+21	1,352	+21 (50 mg.)
	5	657	3,500	-30 (20 mg.)	+47	+68	657	+31 (50 mg.)
	6	—	2,600	—	—	—	958	- 6 (50 mg.)
Mean and S.D.		963 ± 661	3,127 ± 594	-20 ± 7†	+36 ± 8†	+39 ± 21	1,026 ± 635	+19 ± 19
VC (ml.)	1	1,522	4,300	-19	+56	+10	1,597	-11
	2	3,580	4,870	-11	+21	+26	3,475	+38
	3	861	3,260	Respiratory distress			861	-48
	4	2,005	3,140	- 8	+16	+13	2,200	+11
	5	1,680	4,260	+ 6	+32	+61	1,680	+38
	6	—	3,160	—	—	—	1,884	- 4
Mean and S.D.		1,930 ± 1,012	3,332 ± 1,238	- 8 ± 10	+31 ± 18†	+27 ± 24	1,950 ± 869	+15 ± 23
%FEV ₁ /VC	1	43.5		- 1	-17	+18	45.4	+20
	2	56.9		- 8	+ 8	+ 8	58.2	+ 9
	3	41.7		Respiratory distress			41.7	+ 7
	4	56.5		- 6	+11	+ 7	62.5	+ 6
	5	39.1		-33	+12	+ 5	39.1	+ 3
	6	—		—	—	—	50.8	- 3
Mean and S.D.		48 ± 9		-12 ± 15	+ 3 ± 14	+ 9 ± 6	50 ± 9	+ 7 ± 8
PaO ₂ (mm. Hg)	1	73.0		- 1	+ 6	+ 8	73.5	+ 3
	2	65.8		0	+10	+13	76.6	- 1
	3	—		Respiratory distress			—	—
	4	97.0		-13	-11	-12	86.0	+ 6
	5	82.0		-24	-18	-12	87.0	-12
	6	—		—	—	—	—	—
Mean and S.D.		80 ± 13		-10 ± 12	3 ± 14	- 1 ± 14	81 ± 7	- 1 ± 8

CI (L./min./M. ²)	1	—	—	—	—	—	—	—	—
	2	4.48	-28	-34	-21	3.63	-26		
	3	—	—	—	—	4.63	+28		
	4	3.71	+17	+24	-10	3.36	+16		
	5	3.24	-19	-8	-6	3.67	-21		
	6	—	—	—	—	3.36	-10		
Mean and S.D.		3.81 ± 0.6	-10 ± 24	-6 ± 29	-12 ± 8	3.73 ± 0.5	+ 8 ± 22		
PRI (units)	1	—	—	—	—	—	—		
	2	22.3	+34	+46	+19	22.2	-25		
	3	—	—	—	—	25.1	-22		
	4	23.8	-17	-21	+5	25.2	-7		
	5	26.4	+32	+13	+11	23.3	+36		
	6	—	—	—	—	30.7	+46		
Mean and S.D.		24 ± 2	+17 ± 29	+13 ± 34	+12 ± 7	25 ± 3	- 3 ± 24		
MAP (mm. Hg)	1	95.6	0	+8	+12	96.7	+3		
	2	99.1	-2	-1	-4	80.4	+0		
	3	—	—	—	—	113.0	-4		
	4	88.4	-2	-1	-5	84.8	+3		
	5	85.5	+7	+2	+3	85.4	+7		
	6	—	—	—	—	103.0	-8		
Mean and S.D.		92 ± 6	+ 1 ± 4	+ 2 ± 5	+ 1 ± 8	94 ± 13	0 ± 5		
HR/min.	1	86.6	+1	-3	-2	87.0	-1		
	2	84.9	-10	-11	-15	58.9	+10		
	3	—	—	—	—	88.1	-11		
	4	72.1	-11	-18	-23	73.5	-9		
	5	85.0	+1	-1	—	85.0	-9		
	6	—	—	—	—	63.9	-3		
Mean and S.D.		82 ± 7	- 5 ± 7	- 8 ± 8	-13 ± 10	76 ± 13	- 4 ± 8		

FEV₁ = Forced expiratory volume in one second; VC = vital capacity; PaO₂ = arterial PO₂; CI = cardiac index; PRI = peripheral resistance index; MAP = mean arterial pressure; HR = heart rate.

*The sexes, ages, and body surface areas for Subjects 1 to 6, respectively, are: male, 35, 1.86; male, 41, 1.78; male, 59, 1.51; female, 45, 1.74; male, 37, 1.68; female, 59, 2.06.

†Significant difference with p = or <0.01.

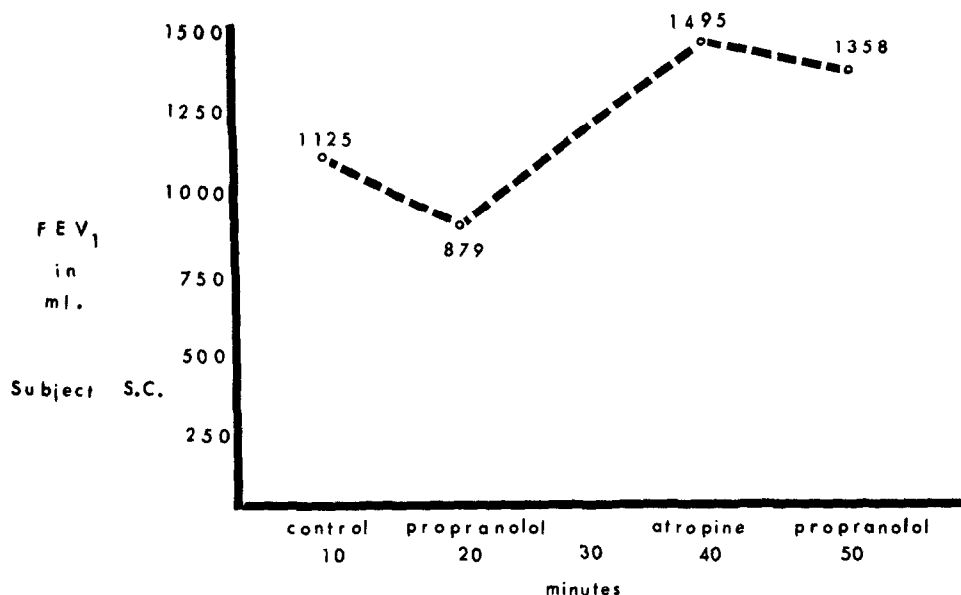


FIG. 1. Typical FEV₁ changes in a single asthmatic patient (Subject 4, S. C.) with intravenous propranolol (20 mg.) before and after an atropine aerosol. Initial FEV₁ was 42 per cent of predicted normal.

DISCUSSION

Propranolol, a beta adrenergic blocking agent, causes a slow contraction of isolated normal human bronchial muscle.⁹ In studies of forced expiratory volume and airway resistance measured by body plethysmography in human asthmatic patients, significant increases in resistance are noted following propranolol, frequently within 2 minutes and usually within 10 minutes.¹⁰⁻¹³ While no effect was noted on the FEV₁ of normal subjects, a similar rise of airway resistance was demonstrated by whole body plethysmography.^{13, 14} This rapid induction of bronchoconstriction in normal human subjects suggests that the mechanism may not be related to the direct slow contraction characteristic of isolated human bronchial muscle.

The administration of intravenous propranolol to 5 asthmatic patients in this study resulted in a significant fall in FEV₁ and a lesser decrease of VC, FEV₁/VC per cent, and PaO₂ within 10 minutes. Heart rate and cardiac index decreased, while mean arterial pressure and peripheral resistance index increased, but the changes were not statistically significant in this small series of patients.

Aerosol atropine sulfate interfered with the propranolol-induced fall of FEV₁, VC, and FEV₁/VC per cent; the FEV₁ decrease was completely reversed in 3 patients studied and reduced in the fourth. Previously, using 1.2 mg. of atropine sulfate intravenously in 4 asthmatic subjects, Macdonald and associates¹³ had demonstrated partial reversal of the expected rise of airway resistance following 5 mg. of intravenous propranolol. Langer¹⁵ and Herxheimer¹⁶ have

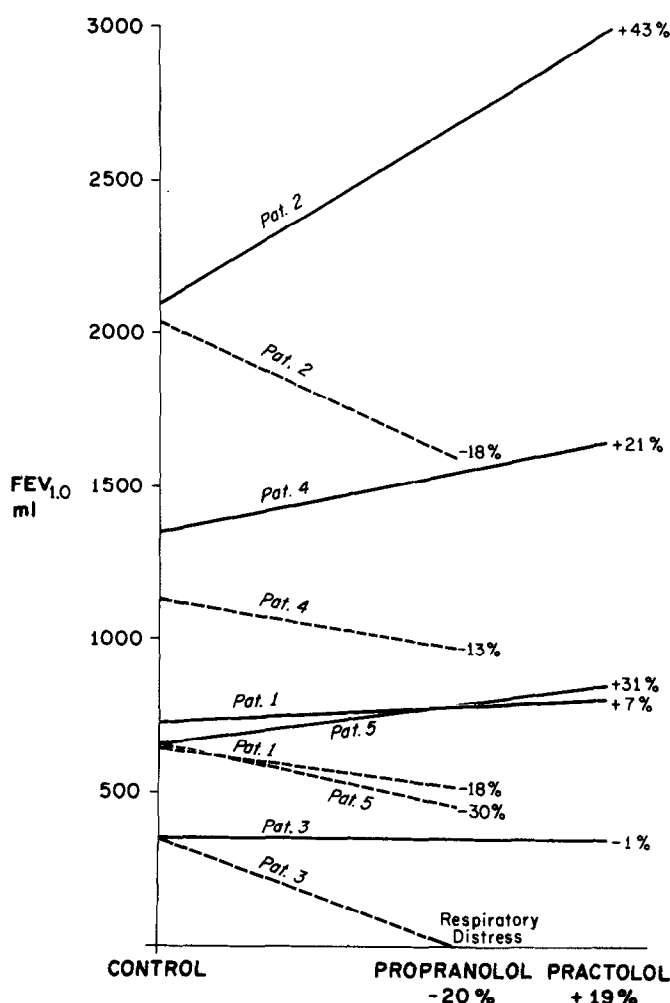


FIG. 2. Divergent FEV₁ responses to propranolol and practolol in 5 asthmatic patients.

reported atropine antagonism of propranolol aerosol effects in asthmatic patients and guinea pigs, respectively.

These observations suggest that unopposed cholinergic impulses are responsible for the bronchoconstriction resulting from propranolol beta adrenergic blockade. The major belladonna alkaloids, including atropine, have two principal actions in the body. The first is in the central nervous system; the mechanism underlying this central action is unknown. The second and more significant is a highly selective blocking action on nerve impulse transmission to effector organs innervated by postganglionic cholinergic nerves. All the muscarinic effects of acetylcholine and related choline esters can be prevented by atropine, and many of the responses to postganglionic cholinergic nerve stimulation can also be blocked. The mechanism involved is an increase in threshold of response of the effector cell to acetylcholine.¹⁷

Although less effective than isoproterenol, atropine has been shown to reverse bronchoconstriction associated with aerosol methacholine,¹⁸ dusts,^{19, 20} citric acid aerosol,²¹ hypoxemia,²² occasional cases of exercise-induced asthma,²³ placebo allergens, and nasal and nasopharyngeal irritation with silica particles.²⁴ Cholinergic efferent pathways may be responsible for asthmatic reactions to nonallergic factors such as infection, which may alter bronchial beta adrenergic activity,^{25, 26} and hypersensitive cough receptors.²¹

Practolol is a beta blocking agent described by Dunlop and Shanks²⁷ which differs from propranolol in that it has significant intrinsic sympathomimetic activity and no membrane-stabilizing properties, and it is predominantly cardio-selective. The drug is about $\frac{1}{150}$ as active as propranolol in antagonizing epinephrine-induced relaxation of isolated tracheal chains prepared from guinea pigs, and it does not prevent a fall in arterial blood pressure in response to isoproterenol.²⁷

The administration of intravenous practolol to 6 asthmatic patients in this study resulted in a mean 19 per cent increase of FEV₁, with a decrease in only 2 patients of one and 6 per cent. One patient tolerated 50 mg. of practolol with only a one per cent decrease in FEV₁ but subsequently experienced a respiratory arrest after receiving 3 mg. of intravenous propranolol. Both VC and FEV₁/VC per cent tended to increase, and PaO₂ was variably affected. Previously Macdonald and McNeill²⁸ had demonstrated a mean fall of FEV₁ of 9.2 per cent in a series of 10 asthmatic patients receiving 15 mg. of practolol intravenously over 30 seconds. Although the FEV₁ fell in all 10 patients, airway resistance decreased 4 and 12 per cent in 2 of these subjects. Thus, it appears that practolol can be given intravenously to most asthmatic patients without significant bronchoconstriction. Cardiac beta adrenergic blockade with similar doses of practolol has been demonstrated in previous studies.²⁹ This requires evaluation of response to exercise or beta adrenergic agonists.

Ahlquist's² designation of receptor systems activated by sympathomimetic amines as alpha and beta has been recently augmented by the differentiation of beta receptors into beta-1 and beta-2 by Land and associates³⁰; beta-1 receptors act in lipolysis and cardiac stimulation, and beta-2 receptors initiate bronchodilation and vasodilatation. Practolol, acting as a beta-1 antagonist, fails to block bronchial or peripheral blood vessel beta adrenergic receptors.

Two recent studies suggest that practolol might be a useful adjunct to bronchodilator therapy in the management of bronchial asthma. Powles and associates³¹ have shown in 9 asthmatic patients that this drug successfully blocks the undesirable tachycardia and palpitations following aerosol isoproterenol, without hindering the beneficial bronchial action of the drug. Palmer and associates³² demonstrated that 20 mg. of practolol prevented the fall in PaO₂ in 11 asthmatic patients after isoproterenol, without diminishing the bronchodilator action. A new class of beta adrenergic stimulants, which are long acting due to resistance to catechol-O-methyl transferase metabolism and have a considerably greater action on bronchial as compared to cardiac muscle, should obviate the need for an isoproterenol-practolol combination³³⁻³⁵ in the treatment of asthma. However, the utility of a beta blocking drug effective in treating

arrhythmias and angina, but usually avoiding the induction of bronchoconstriction in asthmatic persons, is obvious.

Thus, two conclusions appear warranted regarding the mechanism of bronchoconstriction due to beta adrenergic blockade:

1. Propranolol-induced bronchoconstriction in intact human asthmatic subjects is reversed by atropine, suggesting that unopposed cholinergic impulses are responsible for constriction.

2. Pulmonary receptors can be differentiated from cardiac beta adrenergic receptors, by selective beta-1 adrenergic antagonists such as practolol, which appear to spare the bronchial tree.

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