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Patterns of responses to bronchodilators in patients with bronchial asthma

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Serial blood gas measurements were obtained in 15 patients with chronic, stable asthma over an average of 72 minutes before a stable state Pa_{O_2} (±2.0 mm. Hg) resulted. There was a mean variation in Pa_{O_2} of ±11.3 mm. Hg, with 75 per cent of the patients demonstrating a 7.0 mm. Hg or more change. Interpretation of subsequent bronchodilator drug-induced Pa_{O_2} changes must account for these significant time-associated variations. A significant change in Pa_{O_2} over the control period variation ($p = < 0.05$) developed in 12 patients after 0.75 mg. of aerosol isoproterenol. Six patients exhibited a fall in Pa_{O_2} at 6 minutes and were characterized by a higher control $\dot{V}_{O_2}$ ($p = < 0.05$) which was unchanged after isoproterenol. In 6 other patients Pa_{O_2} rose; here lower control Pa_{O_2}, $FEV_{1.0}$ (forced expiratory volume), FVC (forced vital capacity), and $\dot{V}_E$ (minute ventilation) and a more than greater response in bronchodilation and heart rate, alveolar ventilation, and $\dot{V}_{O_2}$ were observed. Aerosol isoproterenol and intravenous aminophylline were combined and induced a change in the Pa_{O_2} equivalent to that seen with isoproterenol **alone.** Repeated aerosol isoproterenol dosing to 4 patients (average total dose, 2.18 mg.) over a mean of 41 minutes did **not** result in progressive hypoxemia. An initial Pa_{O_2} fall was followed by Pa_{O_2} elevation and return to control levels despite continued drug administration; cardiovascular responses followed similar trends. The implications of these findings are discussed.

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Isoproterenol and aminophylline may cause a reduction in the arterial blood oxygen tension (Pa_{O_2}) despite reductions in airway obstruction and respiratory work.[1-4] The present investigation examines selected aspects of this pharmacologic problem which have not been clearly delineated before. Analysis of the variations in the arterial blood-oxygen tension during a control period is stressed for more meaningful interpretation of subsequent bronchodilator-induced Pa_{O_2} change. Consideration was also given to the temporal sequences during induction and recovery from induced Pa_{O_2} changes. Additionally, in severe status asthmaticus, combination aerosol isoproterenol and intravenous aminophylline are frequently employed. Since these drugs have been reported to produce both similar or dissimilar effects upon Pa_{O_2}, their combined administration was evaluated. Finally, the possible toxic potential of isoproterenol-induced hypoxemia was evaluated by repetetive isoproterenol dosing under controlled conditions.

Materials and methods

A. Patient selection. Fifteen patients with moderately severe bronchial asthma were selected. Eleven were in a chronic stable state of no perceptible wheezing (stable) to minimal symptoms (mild asthma); 4 patients were studied during an acute asthmatic attack. One patient was studied on 2 occasions. The diagnosis was established by a clinical history of continuous or episodic wheezing and dyspnea, allergic diathesis, improvement in simple breathing mechanics (mean 15 per cent in FVC or $FEV_{1.0}$) following aerosol isoproterenol, blood and sputum eosinophilia, and the absence of criteria of chronic bronchitis or emphysema, by clinical, radiologic, and physiologic parameters. Most of the patients were nonsmokers who had pulmonary symptoms for several years. All isoproterenol and aminophylline preparations were discontinued at least 12 hours prior to the study.

B. Procedure.

1. PHYSIOLOGIC TESTING. All arterial blood gas studies were conducted in the supine position with an indwelling plastic cannula. A *control stable state* was defined by following serial arterial oxygen and carbon dioxide tensions until 2 to 3 sequential values *agreed within 2 to 3 mm. Hg tension.* Heparinized arterial blood was analyzed within 2 to 4 minutes (on ice) in the Instrumentation Laboratories analyzer.

Spirometry employed an Air Shields spirometer and included: forced vital capacity (FVC), forced expiratory volume at one second ($FEV_{1.0}$), and $FEV_{1.0\ per\ cent}$ observed and predicted, all values BTPS (body temperature and pressure, saturated).

Expired gas was collected in a meterologic balloon from a one-way closed system over the last 2 minutes of a 6 minute test period, the volume measured by a precalibrated respirometer; CO_2 and O_2 were analyzed by the Scholander method. Alveolar oxygen partial pressure ($P_{A_{O_2}}$), alveolar ventilation ($\dot{V}_A$), physiologic dead space to tidal volume ratio (V_D/V_T), CO_2 output ($\dot{V}_{CO_2}$), oxygen consumption ($\dot{V}_{O_2}$), alveolar-arterial P_{O_2} gradient (A-a P_{O_2}), and minute ventilation ($\dot{V}_E$) were determined.

2. AEROSOL ADMINISTRATION. Once control steady state Pa_{CO_2} and Pa_{O_2} levels were established, as defined above, 10 inhalations of isoproterenol (0.075 mg. per inhalation) were delivered from a standard freon-propelled unit in a mainstream adapter; the first 6 inhalations were given over 2 minutes and then 4 inhalations over the following 2 minutes. Arterial samples were collected every 1 to 2 minutes for 15 to 20 minutes and then every 3 to 4 minutes until the Pa_{O_2} returned to its original or new steady state level as defined by no more than a 2 to 3 mm. Hg Pa_{O_2} or Pa_{CO_2} change. All cited physiologic parameters were restudied within 6 minutes of the initial dose. Concurrent observations of pulse, blood pressure, and ECG were conducted.

3. REPETETIVE ISOPROTERENOL ADMINISTRATION. Four patients under steady state Pa_{O_2} and (Pa_{CO_2}) conditions received 10 inhalations of isoproterenol followed by 2 inhalations every 3 minutes for a total average duration of 41 minutes. Serial blood analyses were performed

Table I. Control period Pa_{O_2}

Patient	*Clinical state*	*Age (yr.)*	*Sex*	*Weight (Kg.)*	*Height (cm.)*	*Control time (min.)*	*Mean Pa_{O_2} (mm. Hg)*	*Pa_{O_2} range (mm. Hg)*
MJ	Mild asthma	67	M	88.6	169	103	64	61- 68
BH	Stable	49	F	65.0	160	104	86	80- 93
EK	Mild asthma	45	F	61.4	170	71	79	74- 86
JL-1	Stable	24	F	59.0	162	67	95	86-101
AT	Mild asthma	39	F	60.0	168	96	78	62- 90
JB	Mild asthma	45	M	76.4	165	68	77	73- 82
GSt	Acute attack	35	F	65.9	152	25	74	72- 75
SC	Stable	29	F	62.7	157	81	98	95-100
GH	Mild asthma	50	F	86.4	163	95	75	67- 85
JL-2	Stable	24	F	59.0	162	94	91	89- 95
CS	Mild asthma	31	F	54.1	168	82	57	50- 64
SA	Mild asthma	24	M	70.0	178	138	56	53- 71
LM	Mild asthma	63	M	77.3	168	48	63	59- 71
AV	Acute attack	62	M	65.9	170	32	70	64- 79
DS	Acute attack	43	M	80.0	175	26	61	60- 61
GSd	Acute attack	25	F	49.5	160	52	70	69- 77
	Average					72.4	74.8 ± 12.6*	68- 79

*Mean and standard deviation.

approximately every 2 to 3 minutes until a new steady state was reached. Blood pressure, clinical, and ECG monitoring were continuous. The mean total dose received was 2.18 mg. of isoproterenol which constituted an average of 29 inhalations.

4. AMINOPHYLLINE AND ISOPROTERENOL. After a new control level was obtained (as defined above), 250 mg. of aminophylline was administered intravenously over a 5 to 10 minute period to 5 patients. After several minutes period of time a maximum effect in Pa_{O_2} resulted; aerosol isoproterenol (10 doses over 2 minutes) was then added, and the subsequent blood gas changes followed serially.

Results

A. Control period observations. A mean Pa_{O_2} of 74.8 ± 12.6 mm. Hg (1 S.D.) was observed in 15 patients; this was based upon 119 *serial* samples over an average of 72 minutes until a stable Pa_{O_2} (±2.0 mm. Hg developed (Table I). The mean variation in the base-line Pa_{O_2} was striking with an average range of 11.3 mm. Hg, but included changes from 1.0 mm. Hg to as much as 28.0 mm. Hg: in 75 per cent of the subjects, there was a 7 mm. Hg or more variation. The time necessary for a steady state varied from 25 to 138 minutes. This period was occasionally associated with cough, position change, deep breathing, intercurrent wheezing, or spirometric testing, but, otherwise, the patients were at rest, exposed only to the arterial sampling. A lower control Pa_{O_2} was associated with a higher V_D/V_T ratio ($r = -0.86$), greater A-a Po_2 gradient ($r = -0.92$) and lower FVC ($r = +0.74$).

B. Aerosol isoproterenol effect. Because of the variations noted during the control period, patient movement, spontaneous coughing, deep breathing, or performance of spirometric testing were minimized during isoproterenol study.

Table II. Changes occurring after 10 inhalations of isoproterenol

Patient	Pa_{O_2} *control*	Pa_{O_2} *(6 min.)*	Pa_{O_2} *(20 min.)*	*Amount* FEV_1 *(L.)*	*Amount* *FVC (L.)*	*Amount* Pa_{CO_2} *(mm. Hg)*
Group I:						
MJ	63.9 ± 2.4	56	61	NA‡	NA	-1
BH	85.7 ± 3.9	69	82	+0.31	+0.38	-3
EK	78.6 ± 2.7	70	85	-0.42	-0.33	0
JL-1	94.4 ± 5.6	79	NA	+0.50	+0.42	-4
AT	78.5 ± 7.8	67	75	+0.18	+0.22	+0.5
JB	76.8 ± 2.9	71	72	+0.27	+0.07	-3
Mean	79.6 ± 10.9	68.7*	75.0	+0.17 (11.3%)	+0.15 (6.9%)	-1.75 (6.3%)
Group II:						
SC	97.6 ± 2.3	101	78	+0.15	-0	-2
GH	75.2 ± 5.5	87	55	+1.27	+1.23	-5
JL-2	90.0 ± 2.0	102	90	+0.62	+0.42	+2
CS	57.3 ± 4.0	64	45	+0.95	+1.30	-2
SA	55.8 ± 1.9	67	62	+0.62	+1.08	-1
LM	63.2 ± 1.5	69	57	+0.55	+0.83	-3
Mean	71.8 ± 15.2	81.7*	64.5	+86 (81.9%)	+0.81 (44.0%)	-1.87 (6.5%)

*p = < 0.05.
†R.Q. = Respiratory quotient.
‡NA = Not available.
Figures in parentheses indicate percentage change from control.

Following 10 aerosol doses of isoproterenol to 12 patients, 2 Pa_{O_2} responses were observed (Table II). Six patients (Group I) demonstrated a significant maximum mean Pa_{O_2} *fall* of 10.9 mm. Hg at 6 minutes returning to control values by 20 minutes ($p = < 0.05$). Group II (6 patients) exhibited a maximum mean *rise* in the 6 minute Pa_{O_2} of 9.9 mm. Hg, again significantly above the base-line variation ($p < 0.05$). There was a mixed response, however, by 20 minutes with the Pa_{O_2} lower in 4 and greater or no change in 1 subject each when compared with the control values.

In Group I there was a higher control period Pa_{O_2}, $FEV_{1.0}$%, FVC, $\dot{V}_E$, and $\dot{V}_A$ that was not statistically significant ($p > 0.05$) (Table III). With either change in Pa_{O_2} after isoproterenol, $\dot{V}_E$ and $\dot{V}_A$ improved ($p < 0.05$) and Pa_{CO_2} fell *equally* in both groups (Table II). Control oxygen uptake was significantly higher in Group I ($p < 0.05$) (Table IV). The mean height and weight of the patients in each group were similar, although Group II was slightly younger by 8 years. The increase in $\dot{V}_{O_2}$ after isoproterenol was greatest in Group II.

Patient JL, studied twice, demonstrated dissimilar Pa_{O_2} responses. In the first study, a 6 minute Pa_{O_2} elevation was noted (Group II). A second study, however, revealed only a Pa_{O_2} fall (Group I).

C. Repetetive isoproterenol administration (Fig. 1). Four patients of Group I with *repeated* isoproterenol dosing re-exhibited a fall in Pa_{O_2}, but progressive

of change noted (6 minutes)							
$\dot{V}_E$ *(L./min.)*	$\dot{V}_A$ *(L./min.)*	$\dot{V}_{CO_2}$ *(ml./min.)*	$\dot{V}_{O_2}$ *(ml./min.)*	V_D/V_T *(per cent)*	*R.Q.*†	*A-a*O_2	*Heart rate*
-1.40	-0.81	-30.71	-25.7	+4	-0.03	+5.99	+5
+1.07	+1.80	+18.10	-27.9	-1	+0.18	+19.1	+31
+1.22	+1.14	+35.4	+37.5	-2	+0.03	+7.00	+16
+2.22	+0.92	+30.5	+15.5	+4	-0.11	+11.60	+13
+3.17	+2.03	+48.4	+14.4	-4	+0.25	+3.10	+13
+1.41	+0.81	-5.0	-35.5	-3	+0.10	+10.40	+12
+1.28*	+0.98*	+16.1*	-3.6	-0.3	+0.07	+9.53	+15
(16.8%)	(17.9%)	(9.1%)	(1.6%)	(-1.1%)	(8.9%)	(24.9%)	
+0.19	-0.29	-6.0	-23.7	+11	-0.10	-0.40	+55
+5.37	+4.11	-128.3	+86.5	-12	+0.24	-0.30	NA
+1.97	+0.85	+33.5	+3.5	+8	+0.17	-9.70	+25
+4.05	+3.52	+71.3	+54.4	-10	+0.13	+5.30	+30
+3.14	+2.48	+62.8	+35.0	-2	+0.15	-2.30	+13
+0.47	+1.25	+26.2	+7.4	-11	+0.11	-1.30	+30
+2.53*	+1.99*	+52.7*	+27.1	-2.7	+0.11	-1.45	+31
(43.9%)	(47.8%)	(38.9%)	(16.0%)	(-10.8%)	(13.6%)	(-3.6%)	

hypoxemia did not develop and a rise in Pa_{O_2} occurred *despite* continuous dosing. The magnitude of this reduction in Pa_{O_2} was approximately the same as with the single unit dosing. Cardiac rate and blood pressure followed a similar pattern. Continuous ECG monitoring revealed an occasional extrasystole. Increases in $FEV_{1.0}$ (0.27 L.) and FVC (0.22 L.), and small decreases in Pa_{CO_2} (2.7 mm. Hg) were noted.

D. Combined aminophylline and isoproterenol administration. Ten aerosol doses of isoproterenol were delivered to 5 patients at the point of maximum aminophylline Pa_{O_2} increase (Fig. 2). The average time necessary for maximum aminophylline Pa_{O_2} response was 23 minutes. In 3 patients who previously manifested hypoxemia with isoproterenol, its concomitant administration with aminophylline *still* induced hypoxemia within 6 minutes. In general, the absolute effect of isoproterenol alone versus that in combination resulted in a final Pa_{O_2} of the same order of magnitude. Two patients of Group II similarly exhibited further increases in Pa_{O_2} with the 2 agents.

Discussion

The present data are in agreement with reports of reduced arterial oxygen tensions during chronic, stable bronchial asthma, with a mean Pa_{O_2} of 76.1 ± 13.6 mm. Hg.[5] Additionally, a great variability in serial Pa_{O_2} during a control period

Table III. Control and postisoproterenol values

Patient group	Pa_{O_2} *(mm. Hg)*	Pa_{CO_2} *(mm. Hg)*	*pH*	V_D/V_T *(per cent)*	$\dot{V}_E$ *(L./min.)*
Group I:*					
Control	79.6 ± 10.9	28.0	7.42	26.5	7.60
		±3.2	±0.04	±9.6	±1.9
Postisoproterenol	68.7	26.4	7.43	26.0	8.77†
		±3.4	±0.10	±9.0	±0.47
Group II:*					
Control	71.8 ± 15.2	29.0	7.42	25.0	±5.76
		±3.8	±0.04	±10.5	1.4
Postisoproterenol	81.7	27.8	7.44	22.0	8.07†
		±2.6	±0.02	±6.0	±2.37
Mean for all 12 patients (Groups I and II)					
Control	76.1 ± 13.6*	28.5	7.42	25.7	6.68
Postisoproterenol	75.2	27.1	7.43	24.0	8.42

*Mean and 1 S.D.
†$p = < 0.05$.

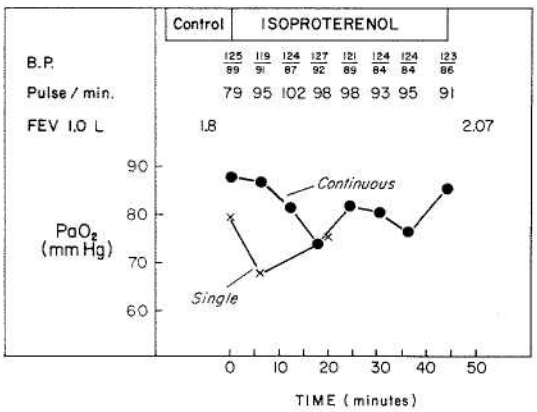

Fig. 1. Effect of repetetive isoproterenol administration. Mean values for 4 patients are presented. The 4 patients received an average of 29 repeated doses for a mean time of 41 minutes (continuous on graph). A fall in Pa_{O_2} of the same magnitude as with single unit dosing (10 inhalations over 4 minutes) occurred. The Pa_{O_2}, however, returns to control levels under both conditions. Heart rate and blood pressure changes were not progressive. See text.

is demonstrated. This variation may be attributed to pulmonary function testing,[6] deep breathing,[7] changes in body position,[8] coughing paroxysms, anxiety during blood sampling, persistent peripheral airway abnormalities not reflected in mouth measurements of airway resistance,[4] and dynamic, temporal, regional variations in ventilation and perfusion characteristics of asthma.[10, 11] These factors are best minimized during this control phase to permit stabilization of Pa_{O_2} (within ±2 to 3 mm. Hg), and thus facilitate the interpretation of subsequent bronchodilator

$\dot{V}_A$ (L./min.)	A-a P_{O_2}	$\dot{V}_{CO_2}$ (ml./min.)	$\dot{V}_{O_2}$ (ml./min.)	R.Q.	FVC (L.)	Per cent Pred FVC	$FEV_{1.0\ per\ cent}$
5.48	38.2	177.2	224.9†	0.78	2.16	57.8	69.8
±1.2	±6.2	±49.2	±49.3	±0.10	±0.47	±18.1	±14.5
6.47†	47.8	193.3	221.3	0.85	2.42	66.8	68.2
±1.1	±4.4	±23.8	±34.2	±0.07	±0.72	±21.9	±8.4
4.16	40.4	135.5	169.2†	0.81	1.84	50.8	53.2
±0.9	±16.0	±20.8	±34.6	±0.06	±0.84	±28.8	±19.8
6.15†	42.7	188.2	196.3	0.92	2.65	75.2	65.7
±1.7	±17.2	±56.1	±63.8	±0.08	±0.38	±16.7	±13.4
4.82	39.3	156.3	197.0	0.79	2.00	54.3	61.5
6.31	45.2	190.7	208.8	0.88	2.53	71.0	67.9

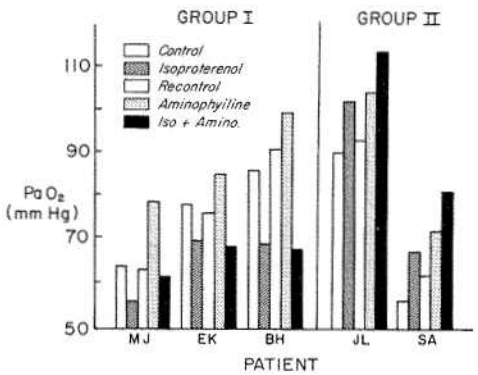

Fig. 2. Combined bronchodilator effect; aminophylline and isoproterenol. Ten doses of isoproterenol were administered to 5 patients at the point of maximum aminophylline Pa_{O_2} elevation. Three patients of Group I (Pa_{O_2} with isoproterenol alone) still exhibited a fall in Pa_{O_2} at 6 minutes despite the initial action of aminophylline. Patients of Group II (Pa_{O_2} with isoproterenol alone) show a cumulative increase in Pa_{O_2}. The control Pa_{O_2} represent the mean values. See text.

effect. The high correlation between a low Pa_{O_2} during the *control period* and a decrease in FVC and an increased V_D/V_T ratio and A-a Po_2 gradient is consistent with the reports of others that a low ventilation to perfusion ratio ($\dot{V}_A/\dot{Q}_C$) is the mechanism of hypoxemia.[3, 12]

Few investigations have emphasized the temporal Pa_{O_2} relationships following isoproterenol.[13-15] The maximal reported Pa_{O_2} change within 10 minutes is similar to that observed in our series and is consistent with the short-lived hemo-

Table IV. Oxygen consumption—mean values for control and postisoproterenol

	Height (cm.)	*Weight (Kg.)*	*Age (yr.)*	$\dot{V}_{O_2}$ *(ml./min.)*	$\dot{V}_{O_2}$ *(ml./min./M.²)*	$\dot{V}_{O_2}/\dot{V}_E$ *(ml./M.²/L.)*
Group I:	165.7	68.4	45			
Control				224.9	127.0	17.3
Postisoproterenol				221.3	125.5	14.3
Group II:	166.0	68.2	37			
Control				169.2	96.1	17.2
Postisoproterenol				196.3	111.1	13.8

dynamic effects of this drug. Dynamic Pa_{O_2} fluctuations, however, continue for 20 to 30 minutes. In our study, differences noted in the 6 minute Pa_{O_2} following 0.75 mg. of isoproterenol may be in part the result of the method of temporal sampling incorporated in our experimental protocol. This may especially be true in regard to patient JL. At 20 minutes, there were individual patients within each group who demonstrated Pa_{O_2} values above and below the control levels.

The change in Pa_{O_2} following isoproterenol was associated with increases in $\dot{V}_E$ and $\dot{V}_A$, bronchodilation, and tachycardia and was greatest in Group II. Effective alveolar ventilation, indexed by Pa_{CO_2}, was similar in the 2 groups. The fact that isoproterenol itself can cause increases in ventilation has been reported by others.[2, 3] Since hyperventilation,[16] maldistribution of inspired air,[2] or redistribution of pulmonary blood flow[13] can alter oxygen transfer, our data are also consistent with a shift in ventilation/perfusion ratios due to physiologic shunting. This effect is over and above the net increases in minute or alveolar ventilation (in liters per minute or effective $\dot{V}_A$ by Pa_{CO_2}).

It is of interest that the patients who demonstrated a fall in Pa_{O_2} (Group I) could be retrospectively distinguished by a significantly higher control period $\dot{V}_{O_2}$. While not commented upon, a similar difference in $\dot{V}_{O_2}$ has been noted by Tai and Read.[13] This difference cannot be accounted for by variations in body size or degree of hyperventilation. Increases in $\dot{V}_{O_2}$ with hyperventilation have been attributed to hypocapnia and systemic alkalosis.[17] Although the control $\dot{V}_E$ was greater in Group I, the $\dot{V}_{O_2}/\dot{V}_E$, Pa_{CO_2}, and pH were similar. Furthermore, a greater work or oxygen cost of breathing in Group I patients seems unlikely in view of the higher $FEV_{1.0}$, FVC, and $FEV_{1.0\ per\ cent}$. Following isoproterenol, a greater $\dot{V}_{O_2}$ increase was noted in Group II while little change occurred in Group I. A similar $\dot{V}_{O_2}$ response to isoproterenol has been documented by others.[2, 13] The greater change in ventilation and R.Q. noted in Group II cannot explain the difference in $\dot{V}_{O_2}$.[18] The pH and Pa_{CO_2} were likewise similar in the 2 groups. Furthermore, the fact that 1 subject (patient JL) responded differently on retesting could suggest dynamic features to the observed responses. These responses may not necessarily be patient specific, but may vary with time. Thus, the differences in the control period and postisoproterenol $\dot{V}_{O_2}$ remains unex-

plained and most likely represents a complex interaction of several factors affecting mechanical work of breathing and cell respiration.

The administration of aerosol isoproterenol at a maximal Po_2 increase due to aminophylline still induced a subsequent rise or fall in Pa_{O_2} *independent* of this aminophylline effect. The magnitude of this change was greater than with isoproterenol alone, but the final Pa_{O_2}, due to cumulative drug effect, was again in the range of that seen with isoproterenol alone. Therefore, despite centrogenic hyperventilation, bronchodilation, improved alveolar ventilation, and resulting rise in Pa_{O_2} by aminophylline, the net β-adrenergic effects of isoproterenol predominate in a given patient with reductions or further elevations in Pa_{O_2}. Consequently, the combined use of these two bronchodilators of different action would appear to offer no necessary protection against the induction of hypoxemia in certain patients with bronchial asthma, although no greater danger in Pa_{O_2} fall would be anticipated.

Although our observations are limited, continuous aerosol isoproterenol did not lead to progressive or persistent hypoxemia or cardiovascular effects. Mechanisms to explain this phenomenon can only be surmised,[19, 20] but may include the formation of a circulatory metabolite with β-adrenergic inhibitory properties[21] which may result in Pa_{O_2} increases.[22] This observation seems pertinent in view of reported increases in the mortality from bronchial asthma which has incriminated overzealous use of pressurized isoproterenol aerosols[23, 24] with hypoxemia and tachyarrhythmias as critical factors.[23, 25-28] Our findings in chronic stable asthma of nonprogressive arterial hypoxemia despite prolonged dosing suggest the lethal mechanism may be more cardiogenic than hypoxemic induced. This interpretation, however, depends largely upon the relationship of oxyhemoglobin affinity and the position along the oxyhemoglobin saturation curve in each individual case. Any level of oxygen saturation falling on the steep portion of the oxyhemoglobin dissociation curve will be more depressed due to any further decrease in arterial oxygen tension than if the initial oxygen saturation were higher. Further observations in the acute and status state, therefore, are needed to clarify this important issue.

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