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Comparison of the effect on blood gases,
ventilation, and perfusion of isoproterenol-
phenylephrine and salbutamol aerosols in
chronic bronchitis with asthma

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The effects of isoproterenol-phenylephrine were compared with those of salbutamol in 11 patients with chronic bronchitis with asthma and at least 20 per cent reversibility of airways obstruction. Among the variables measured, isoproterenol-phenylephrine produced the following significant changes: rise in arterial oxygen tension (P_{aO_2}) accompanied by a fall in carbon dioxide tension (P_{aCO_2}), increase in CO_2 output, and decrease in dead space-tidal volume ratio. Salbutamol, on the other hand, produced a significant fall in oxygen tension (P_{aO_2}) without change in carbon dioxide tension (P_{aCO_2}). Within the limitations of the indirect Fick CO_2 method, there was no apparent difference in the increase of cardiac output produced by the two preparations. The evidence presented suggests that salbutamol caused deterioration in ventilation-perfusion relationships with resultant increase in hypoxemia due to the redistribution of pulmonary blood flow. In contrast, the absence of increased hypoxemia with isoproterenol-phenylephrine would appear to be due to phenylephrine opposing the vasodilator action of isoproterenol, thus preventing disturbance of the homeostatic mechanism. Falls in arterial oxygen tension may occur with salbutamol but are unlikely after inhalation of isoproterenol-phenylephrine. The present results suggest that, in contrast to salbutamol, for the same degree of bronchodilation the changes in blood gases with isoproterenol-phenylephrine represent an improvement in the physiologic state of the patients studied and may give an additional margin of safety when aerosol bronchodilator therapy is used by an already severely hypoxemic patient.

There is well-documented evidence that fall in arterial oxygen tension or saturation may be produced by both sympathomimetic and xanthine bronchodilator drugs in routine use. In order to assess the extent of the falls in

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Pa_{O_2} reported in the literature, a fall of greater than 5 mm. Hg may be taken to be more than twice as great as the probable experimental error in the average laboratory.

On this basis, isoproterenol has been reported to cause falls greater than 5 mm. Hg in 27 of 59 patients (44.3 per cent) studied by Chapman and Hughes,¹ Knudson and Constantine,² Waddell and associates,³ Tai and Read,⁴ Chapman and Dowd,⁵ and Warrell and co-workers.⁶ Similarly, after metaproterenol by subcutaneous injection or inhalation, 20 of 41 (48.7 per cent) of the patients studied by Stiksa and associates,⁷ Meisner and Hugh-Jones,⁸ Daum,⁹ and Chapman¹⁰ showed falls greater than 5 mm. Hg.

After aminophylline by intravenous injection, Halmagyi and Cotes,¹¹ Rees and associates,¹² Tai and Read,⁴ and Rees and co-workers¹³ reported falls in 10 of 38 (26.3 per cent) of their patients. The same authors found falls in 10 of 26 (39 per cent) of their patients after subcutaneous epinephrine.¹⁴

Salbutamol (Ventolin) by inhalation and by intravenous injection produced falls in Pa_{O_2} greater than 5 mm. Hg in 13 of 47 patients (27.6 per cent) reported by Warrell and associates,⁶ Hume,¹⁵ Chapman,^{10, 16} and Bass and associates.¹⁷

In contrast, after inhalation of isoproterenol-phenylephrine (Duo-Medihaler) there were no falls in Pa_{O_2} greater than 5 mm. Hg in 47 patients studied by Chapman,^{10, 16} Hume,¹⁵ and Harris,¹⁸ and in most of these patients a significant increase in Pa_{O_2} and decrease in Pa_{CO_2} was observed. On the other hand, Pflug and co-workers¹⁹ found falls greater than 5 mm. Hg in 5 of 10 patients showing no reversibility of airways obstruction but no falls over 5 mm. Hg in the 3 patients showing 20 per cent increase in one-second forced expiratory volume (FEV_1) after isoproterenol-phenylephrine.

The present study was undertaken to compare the effects on the blood gases of salbutamol and isoproterenol-phenylephrine, both given by pressurized aerosol to the same group of patients.

PATIENTS

The 11 patients selected for this study all had chronic bronchitis with asthma as defined by the Ciba Guest Symposium²⁰ and the Medical Research Council Report, "Definition and classification of chronic bronchitis."²¹ All these patients had a degree of reversibility of expiratory air flow obstruction as shown by increase in FEV_1 greater than 20 per cent following 0.5 mg. of epinephrine subcutaneously on at least one previous occasion. The patients had used no bronchodilator therapy for at least the previous 12 hours. There were 9 men aged 40 to 65 (mean 58 years) and 2 women aged 44 and 66 (mean 55 years). Basal measurements of variables before administering the appropriate active aerosols were in close agreement on the two occasions with the exception that mean Pa_{O_2} was higher before salbutamol administration.

METHODS

Measurements were made initially, after inhalation of inert propellant, and then 30 minutes after inhalation of two "puffs" of isoproterenol-phenylephrine aerosol (320 μg of isoproterenol and 480 μg of phenylephrine) on one occasion and 30 minutes after 2 "puffs" of salbutamol aerosol (200 μg of salbutamol) on the other occasion.

Measurements were taken at 30 minutes because previous reports²²⁻²⁶ have shown that

both isoproterenol-phenylephrine and salbutamol can be expected to maintain maximum effects for at least 30 minutes after inhalation. Furthermore, any possible adverse effects on ventilation-perfusion relationships which did not persist for 30 minutes would be unlikely to be of clinical importance.

The aerosol was, on every occasion, used under the direct supervision of the investigator. If a patient was not familiar with the device, it was manipulated by the investigator personally. Seven patients used isoproterenol-phenylephrine on the first occasion and salbutamol on the second occasion. The other 4 patients used them in the reverse order. The placebo and isoproterenol-phenylephrine were indistinguishable to observer and patient, but the salbutamol aerosol had a slightly different appearance. The FEV₁ was taken as the best of three attempts on a Vitalograph spirometer. Values were corrected to body temperature and pressure, saturated (BTPS).

Minute ventilation was measured as inspiratory volume ($\dot{V}_I$) over a 5 minute period with a Parkinson-Cowan dry gas meter, and respiratory frequency was recorded simultaneously. $\dot{V}_I$ was converted to expiratory volume ($\dot{V}_E$) by the formula $\dot{V}_E = \dot{V}_I \times FI_{N_2} / FE_{N_2}$ and corrected to BTPS. The patients were allowed to get used to the noseclip and mouthpiece, and measurements were recorded only after $\dot{V}_I$ had become stabilized over a period of at least 3 minutes. Expired air was collected for 5 minutes in a 100 liter Douglas bag using a low-resistance one-way valve and analyzed for CO₂ and O₂. Nitrogen was calculated as $100 - FE_{O_2} - FE_{CO_2}$. Oxygen was measured with a Servomex paramagnetic O₂ analyzer calibrated with oxygen-free nitrogen and room air. Carbon dioxide was measured with an Hilger-IRD infrared CO₂ analyzer calibrated with gases of known CO₂ and O₂ content. Calibration gases were analyzed for CO₂ with a modified Haldane apparatus. Oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_{CO_2}$) were then calculated with correction to STPD.

As the subjects were volunteer outpatients and were required to attend on at least two occasions, it was decided to avoid arterial cannulation and cardiac catheterization because of the potential risk associated with these procedures. Oxygenated mixed venous PCO₂ was therefore measured by a "trial and error" rebreathing equilibration method using CO₂/O₂ mixtures of known composition, until an acceptable plateau was obtained on the rapid CO₂ analyzer tracing.²⁷

Blood gases and hydrogen ion concentration were measured on an IL blood gas analyzer incorporating a Severinghaus type PCO₂ microelectrode and a Clark type PO₂ microelectrode. Samples were taken from the hyperemic earlobe into heparinized capillary tubes and analyzed promptly. The earlobe was rendered hyperemic by vigorous massage for 3 minutes with a cream containing thurfyl nicotinate. Langlands and Wallace²⁸ has reported a close correspondence between the results obtained from gas analysis of blood from the hyperemic earlobe and that taken from the brachial artery, and MacIntyre and associates²⁹ have confirmed these findings with the technique used in the present study. Godfrey and associates³⁰ have also confirmed the reliability of the method and have suggested correction factors. They state that no correction is required for PO₂ but recommend a correction factor of 0.65 mm. Hg to be added to the earlobe PCO₂. Since simultaneous duplicate measurements in our laboratory agree to within ± 1 mm. Hg for both PO₂ and PCO₂ and there is similar agreement between samples taken at 30 and 60 minute intervals, a correction factor of 1 mm. Hg has been applied to the earlobe PCO₂ measurements in this study. Physiological dead space-tidal volume ratio was calculated from the formula, $\dot{V}_D / \dot{V}_E = 1 - (PE_{CO_2} / Pa_{CO_2})$ with correction for valve box dead space of 35 ml. Cardiac output was derived from the Fick principle; that is, $\dot{Q}_T = \dot{V}_{CO_2} / (\bar{C}_{\dot{V}_{CO_2}} - Ca_{CO_2})$ with appropriate temperature and pressure corrections. Blood CO₂ content was derived from the tables of MacHardy.³¹

RESULTS

Table I shows the results for FEV₁, $\dot{V}_{CO_2}$, $\dot{V}_{O_2}$, $\dot{V}_D / \dot{V}_E$ per cent, Pa_{O₂}, Pa_{CO₂}, and $\dot{Q}_T$ after placebo and after each active aerosol. In order to make allowance

TABLE I. Eight variables— PaO_2 , PaCO_2 , $\dot{V}\text{O}_2$, $\dot{V}\text{D}/\dot{V}\text{E}\%$, FEV_1 , $\dot{V}\text{E}$, $\dot{V}\text{CO}_2$, and $\dot{Q}\text{T}$

Subject	PaO_2 (mm. Hg)				PaCO_2 (mm. Hg)			
	Isoproterenol-phenylephrine		Salbutamol		Isoproterenol-phenylephrine		Salbutamol	
	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active
1	77	78	84	80	44.5	43.5	41	41
2	70	74	82	72	50.0	40.0	42	40
3	71	83	82	83	38.5	35.0	40	42
4	65	79	65	60	54.0	47.0	46	48
5	66	76	73	72	44.0	42.5	42	40
6	64	60	72	61	49.0	41.0	45	41.5
7	62	72	75	72	47.0	42.0	47	46
8	50	47	50	51	60.0	62.0	63	63
9	69	74	78	80	38.0	36.0	43.5	43
10	65	66	65	58	49.0	43.0	50	45
11	65	67	71	64	41.0	41.0	44	42
Total	724	776	797	753	515	473	503.5	491.5
Mean	65.8	70.5	72.4	68.4	46.8	43	45.8	44.7

TABLE I. Cont'd

Subject	FEV_1 (liters BTPS)				$\dot{V}\text{E}$ (liters/min. BTPS)			
	Isoproterenol-phenylephrine		Salbutamol		Isoproterenol-phenylephrine		Salbutamol	
	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active
1	1.42	1.97	1.35	1.79	7.20	10.50	9.96	14.07
2	0.99	1.60	1.32	1.59	8.62	7.80	7.88	13.50
3	1.87	2.26	1.80	2.60	10.65	10.27	8.51	10.20
4	0.70	0.81	0.58	0.80	9.30	8.35	8.38	17.30
5	1.66	1.98	1.51	1.82	8.28	9.80	8.62	9.79
6	0.59	0.81	0.59	0.86	6.59	7.41	6.21	7.93
7	1.41	1.69	0.97	1.29	10.36	13.82	10.06	10.58
8	0.54	0.71	0.54	0.76	9.58	8.11	7.33	7.49
9	1.58	1.96	0.97	1.29	9.77	12.87	10.29	10.97
10	0.48	0.75	0.47	0.62	9.93	13.55	10.68	11.46
11	1.16	1.49	0.99	1.19	9.80	13.20	9.60	11.13
Total	12.40	16.03	11.09	14.61	100.08	115.68	97.52	124.42
Mean	1.127	1.457	1.008	1.328	9.09	10.52	8.87	11.31

STPD = standard temperature, pressure, dry; BTPS = body temperature, pressure, saturated.

for changes due to any "placebo effect" of using an aerosol or possible changes due to propellents alone, all base-line measurements were made after each patient had used an aerosol containing propellant only.

Ventilation

Both preparations produced an almost identical and significant ($p < 0.01$) increase in FEV_1 , suggesting that the dosages used were equipotent. $\dot{V}\text{E}$ and $\dot{V}\text{CO}_2$ were also similarly increased after both drugs ($p < 0.05$), without change in $\dot{V}\text{O}_2$. Following isoproterenol-phenylephrine, there was a significant mean decrease in $\dot{V}\text{D}/\dot{V}\text{E}$ per cent ($p < 0.01$), but no significant change in this ratio after salbutamol was observed. Since the $\dot{V}\text{D}/\dot{V}\text{E}$ ratio is dependent on the relationship

$\dot{V}O_2$ (ml./min. STPD)				$\dot{V}_D/\dot{V}E\%$			
Isoproterenol-phenylephrine		Salbutamol		Isoproterenol-phenylephrine		Salbutamol	
Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active
228	330	298	380	33	33	28	31
204	139	231	259	50	44	40	43
240	220	221	225	53	48	50	48
258	226	231	252	57	41	48	56
269	298	270	261	33	30	38	33
216	203	187	207	46	41	37	49
347	414	202	212	56	51	55	50
346	302	363	339	53	52	37	40
187	196	219	252	51	49	52	48
234	292	268	309	55	53	57	50
274	337	281	246	52	50	52	40
2,803	2,957	2,771	2,942	539	492	491	488
254.8	268.8	251.9	267.4	49	44.7	44.6	44.3

$\dot{V}CO_2$ (ml./min. STPD)				$\dot{Q}_T$ (liters/min.)			
Isoproterenol-phenylephrine		Salbutamol		Isoproterenol-phenylephrine		Salbutamol	
Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active
210	304	305	419	5.5	7.5	7.5	9.0
221	178	199	223	4.0	4.0	4.5	7.0
220	212	197	204	7.5	7.0	7.0	7.0
208	227	216	264	4.0	4.0	4.0	6.5
246	269	221	267	4.0	4.0	3.5	4.0
171	180	169	164	4.5	5.0	3.5	4.0
255	350	204	236	9.0	12.0	9.0	14.0
271	220	291	269	4.5	4.5	5.0	4.5
157	218	187	236	5.5	7.5	6.5	7.5
218	280	230	261	7.5	9.5	7.0	5.0
212	309	206	304	5.0	6.5	4.0	4.5
2,389	2,747	2,425	2,847	61.0	71.5	61.5	73.0
217.2	249.7	220.4	258.8	5.6	6.5	5.6	6.6

$P_{E_{CO_2}}/P_{a_{CO_2}}$, the decrease must indicate improved ventilation of areas with low ventilation-perfusion ratios following the use of isoproterenol-phenylephrine.

Blood gases

With isoproterenol-phenylephrine there was a significant mean increase ($p < 0.05$) in $P_{a_{O_2}}$ and a significant mean decrease in $P_{a_{CO_2}}$ ($p < 0.01$). There was no individual fall in $P_{a_{O_2}}$ greater than 4 mm. Hg. In contrast, salbutamol produced a significant mean fall in $P_{a_{O_2}}$ ($p < 0.02$) with no change in $P_{a_{CO_2}}$. There were individual reductions in $P_{a_{O_2}}$ of more than 5 mm. Hg in 4 patients who showed decrements of 10, 11, 7, and 7 mm. Hg, respectively. It is unfortunate that the patients were not in precisely the same state of oxygenation on both occa-

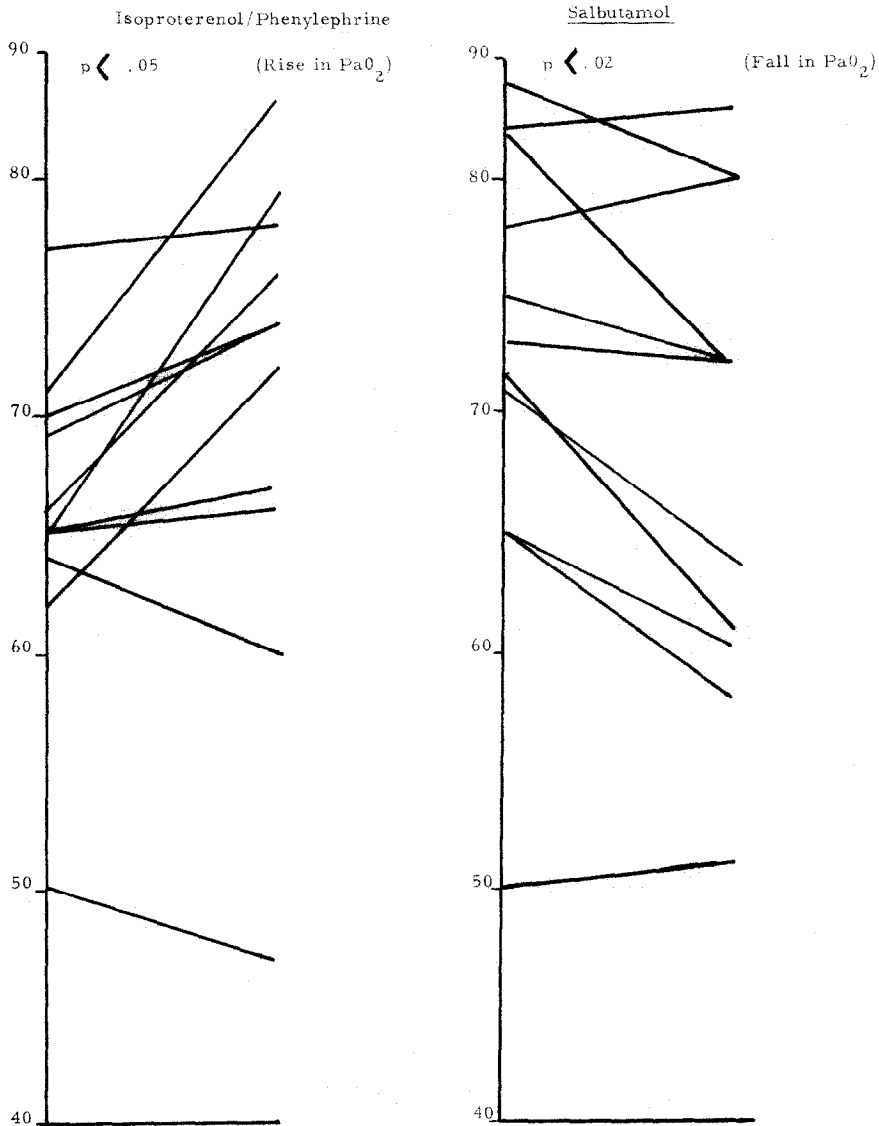


FIG. 1. Changes in arterial oxygen tension (PaO_2 , millimeters of mercury) after inhalation of isoproterenol-phenylephrine and salbutamol by pressurized aerosol.

sions, but the results obtained suggest that the likelihood or degree of fall in Po_2 is not related to the initial level of hypoxemia (Fig. 1).

Cardiac output

Although the indirect Fick CO_2 method may not be entirely reliable in the resting state because of the small mixed venous-arterial CO_2 content difference, the high metabolic rate of these subjects would appear to justify its use in accordance with the views of Warrell and associates.⁶ In each case cardiac output has therefore been rounded to the nearest 0.5 liter and should be considered an approximation. On this basis the mean cardiac output was the same on both

occasions after placebo and showed approximately 16 per cent increase after both isoproterenol-phenylephrine and salbutamol aerosols.

DISCUSSION

The mechanism by which isoproterenol and similar drugs cause a fall in arterial oxygen tension has not been fully established. There is evidence that in some cases of chronic obstructive lung disease there is a reduction of perfusion to underventilated alveoli tending to restore the over-all ventilation-perfusion ratio toward normal.^{1, 7, 9, 10, 11, 16, 32, 33} There is also evidence that the same mechanism influences blood gases in asthmatic patients.^{2-4, 12, 13, 34-41} If the existence of this homeostatic mechanism reducing perfusion to underventilated regions of the lung is accepted, it is then possible to explain the increased hypoxemia produced by beta adrenergic-stimulating drugs as the result of disproportionately increased perfusion. If the increase in perfusion is relatively greater than the increase in ventilation, then there will be an adverse effect on ventilation-perfusion ratios.

Increased perfusion may be due to local pulmonary vasodilation (beta-2 adrenergic effect on vessels) or to increased cardiac output (beta-1 adrenergic effect on myocardium). The work of Palmer and associates,³⁷ which has not yet been confirmed by others, suggests that it may be the latter mechanism which is responsible because of the action of practolol (a selective beta-1 blocking agent which is claimed to affect the myocardium only) in preventing isoproterenol-induced increase in hypoxemia. However, the reported falls in Pa_{O_2} after inhalation of salbutamol are difficult to explain on this basis, since it is claimed that salbutamol, as a result of its selective action on beta-2 adrenergic receptors, has a minimal effect on the myocardium.^{42, 43}

A decrease in oxygenation in the presence of increased ventilation can be accounted for only by an increase in perfusion in excess of ventilation. In the present study there did not appear to be any difference in the effect of the two preparations on cardiac output. It seems reasonable, therefore, to postulate that the increased hypoxemia seen in some subjects following the use of salbutamol is likely to be due to redistribution of pulmonary blood flow. This would not be surprising since pulmonary vasodilation is mediated by beta-2 receptors. The increase in PO_2 after using the isoproterenol-phenylephrine combination suggests that the vasoconstrictor action of phenylephrine opposes the vasodilator action produced by isoproterenol alone.^{44, 45}

The degree of fall in Pa_{O_2} produced by bronchodilators is generally small but may, in some patients, be as much as 15 mm. Hg. It has been estimated that about one in 3 patients may be expected to show a fall of more than 5 mm. Hg following bronchodilator treatment.¹⁸ A recent article⁴⁶ drew attention to the fact that many patients with asthma are in a dangerous physiologic state for long periods. If a patient is on the steep portion of his oxyhemoglobin dissociation curve, a fall in Pa_{O_2} of 5 mm. Hg could be important. If he is already severely hypoxemic, a fall of 15 mm. Hg might be catastrophic by causing rapid, severe desaturation. It is possible that this mechanism may have contributed to the reported increase of deaths in asthma.^{38, 39, 47-49}

Such falls in arterial oxygen tension

unlikely after inhalation of isoproterenol-phenylephrine. The present results suggest that in contrast to salbutamol, for the same degree of bronchodilation, the changes in blood gases with isoproterenol-phenylephrine represent an improvement in the physiologic state of the patients studied and may give an additional margin of safety when aerosol bronchodilator therapy is used by an already severely hypoxemic patient.

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