CHANGES OCCURRING AFTER FREON INHALATION[1]

Investigations of the effects of the inert propellant used in pressurized nebulizers have been limited. Slight reductions in specific airway conductance in normal subjects and patients with asthma[2] and cardiac arrhythmia in hypoxic mice have been reported after the inhalation of propellants.[3] In the present study, changes in arterial blood gases and airway resistance were measured after inhalation of the inert aerosol propellant, Freon (dichlorodifluoroethane with sorbitan trioleate).

The 13 subjects were patients with mild to severe bronchial asthma whose condition was diagnosed by clinical history, allergic diathesis, increase of more than 15 per cent breathing mechanics in forced vital capacity (FVC) or one-second forced expiratory volume (FEV_1) after aerosolized isoproterenol, dermal reactivity, blood and sputum eosinophilia, and the absence of criteria of chronic bronchitis or emphysema. All bronchodilator preparations were discontinued at least 12 hours before the study and no patient was studied during an acute asthmatic attack.

Arterial blood was sampled via an indwelling plastic cannula with the patient in the supine position. After a control stable state, defined as two to three sequential arterial oxygen tension (Pa_{O_2}) and arterial carbon dioxide tension (Pa_{CO_2}) values that agreed within 2 mm Hg to 3 mm Hg, ten inhalations of the inert, aerosol propellant were delivered during four minutes. Blood was collected every one to two minutes for fifteen to twenty minutes and then every three to four minutes until the Pa_{O_2} returned to its original or new steady state level as defined above. After a new steady state was reached, ten inhalations of isoproterenol (0.075 mg per dose) were administered by Freon propellant (Iso-Medihaler®); arterial blood was sampled as for the inert propellant. The electrocardiogram, pulse rate, and blood pressure were monitored during the periods after inhalation of each aerosol.

In 5 patients with mild asthma, airway resistance was measured in a constant volume, whole body plethysmograph.[4,5] One patient

[1] This study was supported in part by grants from the Charlton Fund, Tufts University School of Medicine, Boston, Massachusetts, and Riker Laboratories, Northridge, California.

[2] Sterling, G. M., and Batten, J. C.: Thorax, 1969, *24*, 228.

[3] Taylor, G. T., and Harris, W. S.: J. Lab. Clin. Med., 1970, *76*, 857.

[4] DuBois, A. B., Botelho, S. Y., and Comroe, J. H., Jr.: J. Clin. Invest., 1956, *35*, 327.

[5] DuBois, A. B., Botelho, S. Y., Bedell, G. N., Marshall, R., and Comroe, J. H., Jr.: J. Clin. Invest., 1956, *35*, 322.

TABLE 1

ARTERIAL OXYGEN TENSION IN 13 PATIENTS WITH ASTHMA DURING CONTROL PERIOD

Patient	Age (years)	Sex	Clinical Status	Range of Pa_{O_2} (mm Hg)	Time to Reach Control State (min)
DS	40	F	Mild	79–86	17
CP	50	F	Mild	69–76	35
MV	20	F	Mild	74–76	20
JS	42	M	Severe	65–65	15
WF	44	M	Mild	63–67	20
EJ	61	F	Mild	73–73	15
RF	17	F	Mild	97–106	15
AS	55	M	Moderate	69–75	15
RM	54	F	Moderate	90–93	20
SA	21	M	Moderate	80–95	20
LM	63	M	Moderate	61–65	34
JB	45	M	Moderate	73–82	46
AV	62	M	Severe	59–63	19

(MV) had been studied previously in the manner described above. Slopes were obtained by visual determination on the oscilloscope screen. Thoracic gas volume (Vtg) was measured concurrently and the final results were expressed as airway resistance (Raw) × Vtg. After six to eight control period measurements, five inhalations of a Freon aerosol were administered in one minute. Airway resistance was measured every two to three minutes for the next ten minutes and then every five minutes for the next fifteen to twenty minutes. After a new control period, similar measurements were made after three inhalations of isoproterenol delivered from the standard propellant unit.

During the control period, Pa_{O_2} varied by 0 to 15 mm Hg (mean: 5.3 mm Hg) (table 1). The time necessary to reach this control state averaged 22 minutes.

After the Freon aerosol, the changes in Pa_{O_2} were generally small and occurred within 5 to 15 minutes and returned to control values by 30 minutes (table 2). Although there were greater transient maximal Pa_{O_2} changes, the

TABLE 2

CHANGES IN ARTERIAL OXYGEN TENSION IN 13 PATIENTS WITH ASTHMA AFTER INHALATION OF FREON

Patient	Mean ± SE: Control Pa_{O_2} (mm Hg)	Mean ± SE: Post-Freon Pa_{O_2} (mm Hg)	Maximal Pa_{O_2} (mm Hg)	Maximal Change in Pa_{O_2} (mm Hg)	Maximal Change in Heart Rate (beats/min)
DS	82.3 ± 2.0	79.2 ± 1.2	75	−7.3	+16
CP	72.5 ± 1.5	70.0 ± 1.5	65*	−7.5	0
MV	75.0 ± 1.0	75.0 ± 0.6	77	+2.0	−15
JS	65.0 ± 0.0	65.8 ± 0.7	68*	+3.0	+8
WF	65.0 ± 1.1	65.3 ± 1.3	62	−3.0	+6
EJ	73.0 ± 0.0	72.0 ± 0.5	71*	−2.0	+7
RF	100.7 ± 1.9	101.5 ± 2.0	105	+4.3	0
AS	71.0 ± 1.3	69.6 ± 3.9	65	−6.0	0
RM	91.3 ± 0.9	75.4 ± 2.4*	68*	−23.3	+2
SA	85.0 ± 2.7	88.4 ± 3.5	101*	+16.0	+12
LM	63.2 ± 0.7	66.0 ± 1.1	71*	+7.8	0
JB	76.7 ± 1.0	77.5 ± 1.7	82	+5.3	0
AV	61.0 ± 1.1	63.4 ± 2.2	72	+11.0	+2
Mean ± SE	76.2 ± 1.7	73.2 ± 1.3	75.5		+2.9

*$P = < 0.05$.

TABLE 3

CHANGES IN ARTERIAL OXYGEN TENSION IN 13 PATIENTS WITH ASTHMA AFTER INHALATION OF ISOPROTERENOL-FREON

Patient	Mean ± SE: New Control Pa_{O_2} (mm Hg)	Mean ± SE: Post Isoproterenol-Freon Pa_{O_2} (mm Hg)	Maximal Isoproterenol-Freon Pa_{O_2} (mm Hg)	Maximal Change in Pa_{O_2} (mm Hg)	Maximal Change in Heart Rate (beats/min)
DS	80.0 ± 0.0	78.2 ± 1.9	73*	−7.0	+55
CP	64.3 ± 1.2	63.3 ± 0.9	60	−4.3	+14
MV	70.4 ± 0.8	70.1 ± 2.5	63*	−7.4	+7
JS	60.5 ± 1.3	66.8 ± 0.6*	68*	+7.5	+2
WF	72.0 ± 3.0	65.8 ± 2.8	58*	−14.0	+3
EJ	76.7 ± 0.9	76.6 ± 2.1	83*	+6.3	0
RF	100.7 ± 1.9	99.2 ± 2.3	92*	−8.7	+5
AS	71.0 ± 1.3	68.3 ± 1.5	64*	−7.0	0
RM	72.0 ± 2.2	78.4 ± 1.2*	83*	+11.0	+18
SA	97.0 ± 4.0	94.3 ± 1.2	89	−8.0	+10
LM	60.5 ± 1.5	64.6 ± 1.1*	69*	+8.5	+30
JB	76.7 ± 0.7	71.8 ± 1.7*	64*	−12.7	+20
AV	65.7 ± 3.0	66.3 ± 2.3	76	+10.3	+20
Mean ± SE	72.0 ± 1.6	81.0 ± 2.3	72.5		+14.1

*$P = < 0.05$.

post-Freon period as a whole in all but one patient failed to exhibit any significant differences from the control period. Maximal changes in Pa_{O_2} in 10 of 13 patients were less than 10 mm Hg. Three patients (RM, SA, AV) had considerable changes in Pa_{O_2}. The maximal mean decrease and increase in Pa_{O_2} was 8.1 and 7.0 mg Hg, respectively. The magnitude of the change in Pa_{O_2} after isoproterenol was somewhat greater than after Freon alone (table 3). The maximal mean decrease in Pa_{O_2} was 8.6 mm Hg, and the mean increase was 8.7 mm Hg. Four patients had significant changes during the postisoproterenol period. Also, 10 of 13 showed significant transient maximal changes of Pa_{O_2} that occurred within 5 to 15 minutes, but Pa_{O_2} returned to control values by 30 minutes. Mean heart rate increased 14 beats per min, and pulse pressure increased 10 mm Hg after isoproterenol. Freon inhalation was generally followed by no or small increases in heart rate, which averaged three beats per min, and no change in pulse pressure. Continuous electrocardiographic monitoring revealed no abnormalities except for the occurrence of an occasional premature atrial contraction in 2 patients each after Freon and isoproterenol-Freon inhalation. One patient showed rare premature ventricular contractions after isoproterenol aerosol.

Although there were significant transient changes in maximal airway resistance in some subjects after Freon inhalation, this was not true for the post-Freon period as a whole (table 4). There was a mean increase in Raw × Vtg of 29 per cent and a 75 per cent maximal increase during the post-Freon period. The magnitude of change was similar after isoproterenol inhalation; there was a 55 per cent decrease during the post-isoproterenol period and 67 per cent maximal decrease.

* * *

The blood gas changes occurring after inhalation of Freon in chronic bronchial asthma are, in most cases, small and apparently inconsequential. The responsiveness of the airways to various stimuli is increased in patients with bronchial asthma.[6] In the present investigation, bronchoconstriction or increased airway resistance due to inhalation of Freon caused reductions in Pa_{O_2} in some patients presumably because of alterations in the distribution of inspired air with regional lowering of ventilation/perfusion ($\dot{V}/\dot{Q}$) ratios. In other patients, Freon inhalation seemed to affect inspired air distribution less. If this was accompanied by reflex hyperventilation,[7] coughing

[6] Simonsson, B. G., Jacob, F. M., and Nadel, J. A.: J. Clin. Invest., 1967, *46*, 1812.

[7] Rees, H. A., Millar, J. S., and Donald, K. W.: Lancet, 1967, *2*, 1164.

TABLE 4

MEAN (± SE) CHANGES IN AIRWAY RESISTANCE IN 5 PATIENTS WITH ASTHMA AFTER INHALATION OF FREON*

Patient	Control Period Raw x Vtg (cm H_2O/sec)	Post-Freon Period Raw x Vtg (cm H_2O/sec)	Maximal Post Freon Raw x Vtg (cm H_2O/sec)	Recontrol Period Raw x Vtg (cm H_2O/sec)	Post-Isoproterenol Period Raw x Vtg (cm H_2O/sec)	Maximal Post-Isoproterenol Raw x Vtg (cm H_2O/sec)
BT	11.74 ± 1.0	14.04 ± 1.54	20.04†	12.33 ± 0.88	5.20 ± 0.81†	2.42†
MV	3.35 ± 0.08	3.69 ± 0.22	4.13†	3.47 ± 0.30	2.40 ± 0.35	1.53†
AM	4.48 ± 0.34	5.28 ± 0.71	8.55†	4.94 ± 0.33	4.11 ± 0.22	3.78†
LD	5.07 ± 0.43	5.15 ± 0.61	7.74†	4.14 ± 0.88	2.06 ± 0.24	1.49†
MM	8.11 ± 0.96	11.59 ± 0.95	14.29†	12.98 ± 2.66	4.82 ± 0.17†	4.22†
Mean ± SE	6.26 ± 0.56	8.07 ± 1.43 (29)	10.95 (75)	8.07 ± 0.81	3.66 ± 0.29 (55)	2.69 (67%)

*Figures in parentheses indicate per cent of change.
†$P = < 0.05$.

with clearing of secretions, deep breathing,[8] or compensatory hypoxic pulmonary vasoconstriction,[9] a net increase $\dot{V}/\dot{Q}$ ratio would result and cause an increase in Pa_{O_2}. These mechanisms, however, are conjectural and need better definition. Although it is conceivable that Freon uniquely affects the pulmonary circulation, the relative absence of electrocardiographic, blood pressure, and heart rate changes speaks against a systemic effect similar to isoproterenol.

The addition of isoproterenol to the inert propellant reversed the bronchoconstriction. The subsequent changes in Pa_{O_2} were the result of alterations of not only alveolar ventilation but also pulmonary perfusion.[10-13] Although different mechanisms were operating, the magnitude of Pa_{O_2} change could be similar after inhalation of either aerosol.

[8] Said, S. I., and Banerjee, C. M.: J. Clin. Invest., 1963, *42*, 507.

[9] Hecksher, T., Bass, H., Orial, A., Rose, B., Anthonisen, N. R., and Bates, D. V.: J. Clin. Invest., 1968, *47*, 1063.

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[13] Waddell, J. A., Emerson, P. A., and Gunstone, R. F.: Brit. Med. J., 1967, *2*, 402.

In summary: The inhalation of an inert aerosol propellant by 13 patients with bronchial asthma generally resulted in no sustained significant changes in arterial oxygen tension. The effects noted on the heart rate, blood pressure, and electrocardiogram appeared inconsequential. Increases in airway resistance were noted in 5 patients after inhalation of Freon, but the net effect is that bronchodilation when the inert propellant contained isoproterenol. The magnitude of blood gas changes after inhalation of Freon or Freon-isoproterenol was similar, although different physiologic mechanisms appeared to be operating.

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