Br. J. Pharmac. (1971), **41**, 445–453.

Cardiorespiratory effects of intravenous isoprenaline and salbutamol in dogs

L. LOH, R. F. SEED AND M. K. SYKES

Department of Anaesthetics, Royal Postgraduate Medical School and Hammersmith Hospital, Du Cane Road, London, W12 0HS

Summary

1. The cardiorespiratory effects of intravenous infusions of isoprenaline and salbutamol (1 and 5 μg/min) have been compared in twelve dogs.

2. Both drugs produced a rise in pulse rate, a fall in systemic arterial pressure and a rise in pulmonary arterial pressure. Salbutamol produced a greater increase in cardiac output than isoprenaline.

3. Both drugs produced an increase in venous admixture, but a significant fall in arterial oxygen tension occurred only with isoprenaline at the higher dose.

Introduction

Several reports indicate that administration of isoprenaline may lead to hypoxaemia (Field, 1967 ; Palmer & Diament, 1967 ; Knudson & Constantine, 1967 ; Lockhart, Lissac, Salmon, Zappacosta & Benismail, 1967 ; Tai & Read, 1967 ; Fordham & Resnekov, 1968 ; Chapman, 1969 ; Finlay, Wightman & Sykes, 1970).

It has also been suggested that the increase in the number of deaths due to asthma may be associated with the more frequent use of isoprenaline inhalers (Speizer, Doll & Heaf, 1968 ; Speizer, Doll, Heaf & Strang, 1968). A new potent bronchodilator, salbutamol, has been recently introduced (Brittain, Farmer, Jack, Martin & Simpson, 1968) which, it has been suggested, does not have a significant effect on the cardiovascular system and does not produce a fall in arterial oxygen tension (Palmer & Diament, 1969 ; Palmer, Legge, Hamilton & Diament, 1970). The following experiments were designed to compare the cardiorespiratory effects of isoprenaline and salbutamol in dogs.

Methods

Twelve adult greyhounds (25–35 kg body wt) were anaesthetized with an intravenous injection of 5% thiopentone (25–30 mg/kg) and a cuffed endotracheal tube was passed under direct vision. Anaesthesia was then maintained throughout the 6–8 h of the experiment by a slow intravenous infusion of 600 mg of pentobarbitone in 500 ml of saline. Mechanical ventilation was provided by a Cape ventilator set to give a tidal volume which was adequate to maintain an end-tidal CO_2 concentration of 4·5–5·5% at a frequency of twenty breaths per minute. A pressure operated collect valve (Sykes, 1969) was inserted into the circuit between the Y-piece and endotracheal tube so that the expired gas was not contaminated by the gas compressed in the ventilator tubing.

A catheter was inserted into the abdominal aorta through the femoral artery and another catheter was floated into the pulmonary artery using pressure monitoring to establish its position (Fife & Lee, 1965) (1 mmHg≡1·333 mbar). An arterial blood sample was then analysed to ensure that arterial P_{CO_2} and base excess were within normal limits, any non-respiratory acidosis being corrected by a suitable dose of 4·2% sodium bicarbonate.

When conditions were stable the lungs were inflated three times to a pressure of +30 cm H_2O by occluding the expiratory port of the collect valve, and a set of control readings was obtained on air. An infusion of isoprenaline (1 μg/ml) was then given by a motor driven syringe at a rate of 1 μg/min and after 30 min a second set of readings was obtained. A further set of measurements was obtained 30 min after the infusion rate had been increased to 5 μg/min and the infusion was then discontinued. Sixty minutes later a second set of control readings was obtained and the procedure was repeated with an infusion of salbutamol in doses of 1 and 5 μg/min for similar periods of time.

In six of the twelve dogs additional measurements were made during the inspiration of high concentrations of oxygen so that true right-to-left shunt could be determined. This was accomplished by connecting a Douglas bag containing 5–10% nitrogen in oxygen to the inspiratory port of the ventilator. The bag was continuously refilled from cylinders and after the gas had been inspired for 15 min the gas flow into the bag was shut off, the bag contents were thoroughly mixed and the lungs hyperinflated three times. A set of measurements was made and the Douglas bag was disconnected so that the animal was once again respiring air. This process was repeated after the air measurement at each dose so that comparable measurements of total venous admixture (due to ventilation/perfusion inequality plus right-to-left shunt) and right-to-left shunt were obtained. By subtracting the latter from the former measurement the contribution due to ventilation/perfusion inequality could be obtained.

Each set of observations consisted of measurements of airway pressure, systemic and pulmonary arterial pressures, inspired and expired gas composition and expired gas volume, end-tidal CO_2 concentration and arterial and pulmonary arterial pH and blood gases. Body temperature was measured rectally and expired gas temperature and barometric pressure were also recorded. Expired volumes were measured by a calibrated dry gas meter. Mixed, expired gas was sampled from a mixing unit (Sykes, 1968) and analysed by an infrared CO_2 analyser (Hartmann-Braun Uras 4) and a paramagnetic oxygen analyser (Servomex DCL 101A). Additional gas samples were checked on the O_2 and CO_2 electrodes. Blood gases were determined on two separate CO_2 electrodes (National Welding Corporation and Electronic Instruments Ltd.) and two oxygen electrodes (Radiometer, E 5046). pH was determined on two Radiometer micro-pH electrodes standardized on N.B.S. buffers (Adams, Morgan-Hughes & Sykes, 1967, 1968). A blood gas factor of 1·04 was applied to all blood P_{O_2} readings (Adams & Morgan-Hughes, 1967) and the appropriate temperature correction factors were applied (Kelman & Nunn, 1966). All calibration gases were analysed on a previously calibrated Haldane gas analysis apparatus and the electrodes were checked daily with tonometered blood samples. The calculations, using standard respiratory formulae, were performed on an Elliot 4100 computer using a programme written in this department (Adams, 1970).

Results

Mean values, with their standard errors, for twelve dogs are shown in Tables 1 and 2. The significance of the differences between means (p) was calculated using paired two-tailed Students' t-tests.

Cardiovascular changes

As shown in Table 1 both isoprenaline and salbutamol produced a rise in pulse rate, this rise being greatest with isoprenaline at a dose of 5 μg/minute. Pulsus alternans occurred in half of the dogs given isoprenaline and in only one dog given salbutamol. In the latter animal the irregularity was present at the beginning and persisted throughout the experiment. Systolic, diastolic and mean blood pressures fell progressively with increasing doses of both drugs. Pulmonary artery pressures tended to rise with both drugs, significant increases occurring only with the 5 μg/min dose. At the two doses of 1 μg/min and 5 μg/min salbutamol increased cardiac output by 38% and 91% respectively whereas isoprenaline increased cardiac output only at the 5 μg/min dose by 24%.

Respiratory changes

As shown in Table 2 there was no significant change in tidal volume (V_T) or peak airway pressure (P.A.P.). Both drugs produced approximately equal increases in mean oxygen consumption ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$). The increase in the latter produced an increase in arterial CO_2 tension (P_aCO_2) since tidal volume and the ratio of the dead space volume to tidal volume (V_D/V_T) were unchanged. There were no changes in physiological dead space (V_DPhys) or arterial to alveolar PCO_2 difference (a-APCO_2) with either drug.

There were significant falls in mean arterial oxygen tension (PaO_2) when breathing air at both doses of isoprenaline, but not with salbutamol. The alveolar-arterial oxygen tension difference (A-aPO_2) fell significantly with the 5 μg/min dose of salbutamol but not with isoprenaline, though the mixed venous oxygen tension ($P_{\bar{V}}O_2$) increased significantly with the higher dose of isoprenaline and both doses of salbutamol. Total venous admixture (Q_{va}/Q_t) increased significantly at the higher dose with both drugs but right-to-left shunt (Q_s/Q_t) did not change in the six dogs in which it was measured.

Discussion

The cardiorespiratory effects of bronchodilator drugs should ideally be compared by giving the drugs in a dose which produces an equal degree of bronchodilation. In practice the choice of drug dose is difficult, for the amount of bronchodilation produced depends not only on the dose but also on the route of administration and degree of bronchomotor tone already present. Additional difficulties are presented by the known variations in response to aerosol administration (resulting from variations in delivered dose, site of deposition, and so on) and from the variations in the response of different species to different bronchodilators (Cullum, Farmer, Jack & Levy, 1969). The difficulties inherent in aerosol or oral administration can be avoided by the use of the intravenous route but the evanescent nature of the responses to a single injection would not have permitted accurate measurements of

TABLE 1. *Cardiovascular effects of isoprenaline and salbutamol in twelve dogs*

	C.1. ± S.E.M.	ISO 1 ± S.E.M.	ISO 5 ± S.E.M.	C1/ISO 1 P	C1/ISO 5 P	C.2. ± S.E.M.	SALB 1 ± S.E.M.	SALB 5 ± S.E.M.	C2/SALB 1 P	C2/SALB 5 P	C1/C2
F.A. systolic mmHg	178·4 ±16·1	162·7 ±15·0	153·1 ±16·1	N.S.	0·023	175·7 ±11·4	165·3 ±13·4	160·7 ±10·5	N.S.	N.S.	N.S.
F.A. diastolic mmHg	123·0 ± 6·9	107·8 ± 8·5	101·0 ± 9·6	0·030	0·009	128·4 ± 5·7	112·1 ± 6·5	100·2 ± 8·1	<0·001	0·002	N.S.
F.A. mean mmHg	138·5 ± 8·3	127·4 ±10·2	120·1 ±10·9	N.S.	0·016	135·7 ± 7·3	131·8 ± 7·2	122·1 ± 8·1	N.S.	N.S.	N.S.
P.A. systolic mmHg	20·6 ± 1·1	21·3 ± 1·5	25·2 ± 1·8	N.S.	0·031	25·5 ± 1·4	27·3 ± 1·5	32·0 ± 2·3	N.S.	0·004	0·008
P.A. diastolic mmHg	5·0 ± 1·1	5·4 ± 1·2	7·1 ± 0·9	N.S.	N.S.	7·6 ± 0·8	9·7 ± 0·9	11·5 ± 1·3	0·003	0·002	0·025
P.A. mean mmHg	11·8 ± 0·9	12·9 ± 0·9	15·1 ± 0·9	N.S.	0·001	16·1 ± 0·6	17·2 ± 0·7	20·1 ± 0·9	N.S.	0·001	<0·001
Pulse rate B.P.M.	179·7 ± 5·3	190·5 ± 4·9	206·3 ± 5·8	0·043	0·002	165·7 ± 6·7	176·7 ± 6·1	173·4 ± 7·7	0·027	N.S.	0·047
Cardiac output l/min	4·56± 0·5	4·13± 0·3	5·66± 0·5	N.S.	0·049	3·46± 0·2	4·77± 0·4	6·61± 0·4	<0·001	0·001	0·023

F.A., femoral artery; P.A., pulmonary artery; C.1., control reading before isoprenaline; C.2., control reading before salbutamol; ISO 1, isoprenaline (1 μg/min); ISO 5, isoprenaline (5 μg/min); SALB 1, salbutamol (1 μg/min); SALB 5, salbutamol (5 μg/min). All measurements are given as mean values ± standard errors.

TABLE 2. *Respiratory effects of isoprenaline and salbutamol in twelve dogs*

	C.1. ±S.E.M.	ISO 1 ±S.E.M.	ISO 5 ±S.E.M.	C1/ISO 1 P	C1/ISO 5 P	C.2. ±S.E.M.	SALB 1 ±S.E.M.	SALB 5 ±S.E.M.	C2/SALB 1 P	C2/SALB 5 P	C.1./C.2.
P.A.P. cm H_2O	8·5± 0·3	8·4± 0·2	8·4± 0·2	N.S.	N.S.	8·7± 0·4	8·4± 0·5	7·9± 0·2	N.S.	N.S.	N.S.
V_T ml BTPS	439·2±12·7	425·4±14·4	428·8±13·8	N.S.	N.S.	423·3±14·4	423·6±13·5	427·1±14·0	N.S.	N.S.	N.S.
$\dot{V}_{CO_2}$ ml STPD	184·8± 9·4	175·9± 9·4	209·8±13·0	N.S.	0·016	170·1± 6·6	177·9± 8·5	198·0±10·0	N.S.	0·003	N.S.
$\dot{V}_{O_2}$ ml STPD	206·3±10·0	204·0± 8·9	242·8±14·1	N.S.	0·012	188·6± 7·4	203·9± 8·3	218·7±10·7	0·002	<0·001	N.S.
P_{aCO_2} mmHg	39·3± 0·9	38·1± 0·9	44·8± 1·5	N.S.	0·018	39·0± 1·3	39·8± 1·4	46·4± 1·5	N.S.	<0·001	N.S.
a-AP_{CO_2} mmHg	4·1± 0·7	4·5± 0·5	4·8± 0·6	N.S.	N.S.	4·3± 0·5	3·2± 0·5	3·9± 0·6	N.S.	N.S.	N.S.
V_DPhys ml	191·8± 8·3	182·6± 9·6	184·5± 9·8	N.S.	N.S.	191·1±12·5	185·9±12·0	198·2±11·5	N.S.	N.S.	N.S.
V_D/V_T %	43·9± 1·9	42·9± 1·7	43·2± 2·1	N.S.	N.S.	44·7±2·2	43·7± 2·4	46·3± 2·1	N.S.	N.S.	N.S.
P_{AO_2} mmHg	104·8± 0·9	104·3± 1·3	96·9± 2·2	N.S.	0·005	105·1± 1·6	103·6± 1·6	97·7± 1·9	N.S.	<0·001	N.S.
P_{aO_2} mmHg	93·1± 1·2	90·4± 1·1	84·9± 1·3	0·034	<0·001	90·6± 1·8	89·5± 1·9	87·9± 1·7	N.S.	N.S.	N.S.
A-aP_{O_2} mmHg	11·7± 1·7	13·9± 1·2	12·1± 1·9	N.S.	N.S.	14·5± 1·7	14·0± 1·7	9·8± 1·3	N.S.	<0·001	N.S.
$P_{\bar{v}O_2}$ mmHg	49·0± 1·2	47·5± 1·3	53·1± 1·6	N.S.	0·021	43·3± 1·2	50·2± 1·5	57·9± 1·2	<0·001	<0·001	0·001
$\dot{Q}_{va}/\dot{Q}_t$ %	7·3± 1·1	7·7± 0·9	13·5± 1·8	N.S.	0·008	6·4± 1·1	8·7± 1·6	11·8± 2·7	N.S.	0·039	N.S.
$\dot{Q}_s/\dot{Q}_t$ (n=6) %	4·4± 0·7	4·6± 1·1	5·9± 0·9	N.S.	N.S.	4·5± 0·9	5·3± 0·9	4·5± 1·1	N.S.	N.S.	N.S.

All gas and blood gas tensions expressed as at body temperature. P.A.P., peak airway pressure; C.1., control reading before isoprenaline; C.2., control reading before salbutamol; ISO 1, isoprenaline (1 μg/min); ISO 5, isoprenaline (5 μg/min); SALB 1, salbutamol (1 μg/min); SALB 5, salbutamol (5 μg/min). For all other abbreviations see text. Results given as mean values±standard errors.

cardiorespiratory function. For this reason, in our study the drugs were given by continuous intravenous infusion. Since bronchodilator activity persists longer with salbutamol than with isoprenaline when these drugs are given in a dose which produces the same degree of bronchodilation initially (Farmer & Levy, 1969), it is likely that the continuous intravenous infusion of equal dose rates of these drugs will have resulted in a higher blood concentration of salbutamol. Similar data for dose rates of isoprenaline of 3 and 12 μg/min were already available (Finlay *et al.*, 1970) so that an intermediate and lower dose rate was chosen for the present studies.

Cardiovascular changes

Although salbutamol produced little change in pulse rate it caused a marked increase in cardiac output. Despite this increase there was a reduction in arterial diastolic pressure, indicating a marked reduction in peripheral resistance. Cullum *et al.* (1969) have also noted a reduction in diastolic blood pressure after single doses of 1 and 5 μg/kg salbutamol in dogs but Warrell, Robertson, Howes, Conolly, Patterson, Beilin & Dollery (1970) found little change after intravenous injections of up to (0·24 μg base/kg)/min in man. These authors detected little change in cardiac output in three of the patients given salbutamol and Kelman, Palmer & Cross (1969) found that 200 μg salbutamol given by aerosol had no effect on heart rate or circulation time. Other authors have also commented on the lack of cardiac effects after oral or aerosol administration in humans (Choo-Kang, Simpson & Grant, 1969; Kennedy & Simpson, 1969; Riding, Dinda & Chatterjee, 1970). The difference in the magnitude of the change in cardiac output with salbutamol and isoprenaline may well be related to the slower breakdown and higher blood concentration that were probably achieved during salbutamol administration, but the conspicuous absence of arrhythmias with this drug suggests that it may well deserve a trial as an inotropic drug in man.

Respiratory changes

Arterial hypoxaemia may result from a reduction in alveolar oxygen tension or from an increase in the alveolar to arterial P_{O_2} difference. When the patient is breathing air a reduction in alveolar P_{O_2} is most commonly due to an increase in arterial P_{CO_2}, the increase in the latter being due to a reduction in alveolar ventilation (decreased total ventilation or increased dead space) or to an increase in CO_2 production. An increase in A-aP_{O_2} may be due to an increase in the proportion of venous admixture or to a reduction of the tension of the mixed venous blood which is admixed with the blood leaving properly ventilated alveoli.

In our studies a significant fall in alveolar oxygen tension due to an increased P_aCO_2 occurred only at the higher dose rates with each drug. There was no significant alteration in the ratio of V_D to V_T with either drug so that this fall in alveolar oxygen tension must be ascribed to the increased CO_2 production noted with each drug. Similar changes in metabolic rate have been described by Dodge, Lord & Sandler (1960); Krasnow, Rolett, Yurchak, Hood & Gorlin (1964) and Lockhart, Even, Ourbak, Fernandez, Anguera, Scébat & Lenègre (1966) after the administration of isoprenaline to patients with basically normal lungs. However, in patients with obstructive airways disease Lockhart *et al.* (1967) and Tai & Read (1967) found no increase in oxygen consumption after isoprenaline. This they attributed

to the reduction in the work of breathing resulting from the bronchodilation and reduction in airways resistance.

Both drugs produced a significant increase in the proportion of total venous admixture at the dose of 5 μg/minute. However, the fall in arterial oxygen tension resulting from the change was less with salbutamol than with isoprenaline since there was a greater increase in mixed venous oxygen tension as a result of the higher cardiac output with salbutamol. As a result, the fall in arterial oxygen tension was not significant at either dose rate of salbutamol.

The reduction in oxygen tension following the administration of isoprenaline has most commonly been explained as being due to a reduction in the vasoconstriction which is thought to direct blood away from relatively underventilated alveoli (Field, 1967; Lockhart *et al.*, 1967; Tai & Read, 1967; Fordham & Resnekov, 1968) although Knudson & Constantine (1967) felt that the administration of isoprenaline aerosol to asthmatics would divert still more ventilation to the better ventilated parts of the lung. In support of the former theory Fritts, Harris, Clauss, Odell & Cournand (1958) found that, in emphysematous patients, acetylcholine decreased the oxygen saturation more when the pulmonary artery pressure had been increased by the breathing of 12% oxygen than when the patients breathed air. Furthermore, Haas & Bergofsky (1968) found that generalized pulmonary vasoconstriction, induced by a respiratory or metabolic acidosis, 5-hydroxytryptamine or elevations of extracellular potassium increased arterial oxygen tension. Chapman (1969) has reported falls in oxygen tension with the inhalation of 1% isoprenaline, a mixture of 1% isoprenaline and 2% papaverine, 2% papaverine, orciprenaline and salbutamol but in twelve patients inhaling a mixture of isoprenaline and phenylephrine he found only one patient who suffered a fall in oxygen tension. He therefore concluded that the addition of an α-adrenoceptor stimulating drug (phenylephrine) probably prevented the vasodilatation induced by isoprenaline and so prevented the fall in oxygen tension. It is of interest that in this study a rise in pulmonary artery pressure occurred only with salbutamol and that there was a minimal fall in arterial O_2 tension with this drug; these findings agree with those of Palmer *et al.* (1970) for salbutamol in bronchial asthma patients.

TABLE 3. *Dose-response relationships with isoprenaline and salbutamol (in brackets)*

Dose (μg/min)	1	3*	5	12*
F.A. mean	91 (98)	91	87 (90)	88
P.A. mean	109 (107)	127	125 (125)	191
Cardiac output	89 (138)	159	124 (191)	217
$\dot{V}_{CO_2}$	95 (105)	115	114 (116)	162
$\dot{V}_{O_2}$	99 (108)	117	118 (116)	169
P_{aCO_2}	98 (104)	109	115 (119)	160
P_{aO_2}	97 (99)	95	91 (97)	83
$\dot{Q}_{va}/\dot{Q}_t$	114 (136)	155	200 (185)	423
$\dot{Q}_s/Q_t$	100 (118)	170	150 (100)	157

Changes are expressed as percentage of control reading. * Data from Finlay, Wightman & Sykes (1970).

As can be seen from Table 3, which combines the data of Finlay, Wightman & Sykes (1970) with our studies, all the above-mentioned changes are dose dependent. Equal dose rates of isoprenaline and salbutamol (5 μg/min) produce similar degrees of metabolic stimulation as evidenced by the changes in CO_2 production and O_2 consumption but cardiac output is increased to a greater extent with salbutamol. Again, although the changes in venous admixture are similar, the fall in arterial oxygen tension is much less with salbutamol. These factors, together with the apparently low incidence of arrhythmias suggest that the drug should be further investigated as a possible inotropic agent in the clinical situations in which isoprenaline is at present administered.

REFERENCES

ADAMS, A. P. & MORGAN-HUGHES, J. O. (1967). Determination of the blood–gas factor of the oxygen electrode using a new tonometer. *Br. J. Anaesth.*, **39**, 107–113.

ADAMS, A. P., MORGAN-HUGHES, J. O. & SYKES, M. K. (1967). pH and blood–gas analysis. Methods of measurement and sources of error using electrode systems. Part 1. *Anaesthesia*, **22**, 575–597.

ADAMS, A. P., MORGAN-HUGHES, J. O. & SYKES, M. K. (1968). pH and blood–gas analysis. Methods of measurement and sources of error using electrode systems. Part 2. *Anaesthesia*, **23**, 47–64.

ADAMS, A. P. (1970). The effects of mechanical ventilation on gas transfer within the lung. PhD thesis, University of London.

BRITTAIN, R. T., FARMER, J. B., JACK, D., MARTIN, L. E. & SIMPSON, W. T. (1968). α-[(t-Butylamino) methyl]-4-hydroxy-m-xylene-α^1, α^3-diol (AH 3365): a selective β-adrenergic stimulant. *Nature, Lond.*, **219**, 862–863.

CHAPMAN, T. T. (1969). Bronchodilator aerosols. *Br. med. J.*, **4**, 557.

CHOO-KANG, Y. F. J., SIMPSON, W. T. & GRANT, I. W. B. (1969). Controlled comparison of the bronchodilator effects of three β-adrenergic stimulant drugs administered by inhalation to patients with asthma. *Br. med. J.*, **2**, 287–289.

CULLUM, V. A., FARMER, J. B., JACK, D. & LEVY, G. P. (1969). Salbutamol: a new, selective β-adrenoceptive receptor stimulant. *Br. J. Pharmac.*, **35**, 141–151.

DODGE, H. T., LORD, J. D. & SANDLER, H. (1960). Cardiovascular effects of isoproterenol in normal subjects and subjects with congestive cardiac failure. *Am. Heart J.*, **60**, 94–105.

FARMER, J. B. & LEVY, G. P. (1969). Comparative β-adrenergic stimulant properties of salbutamol (AH 3365), orciprenaline and soterenol (M.J. 1992). *Br. J. Pharmac.*, **35**, 358*P*.

FIELD, G. B. (1967). The effects of posture, oxygen, isoproterenol and atropine on ventilation-perfusion relationships in the lung in asthma. *Clin. Sci.*, **32**, 279–288.

FIFE, W. P. & LEE, B. S. (1965). Construction and use of self-guiding, right heart and pulmonary artery catheter. *J. appl. Physiol.*, **20**, 148–149.

FINLAY, W. E. I., WIGHTMAN, A. E. & SYKES, M. K. (1970). The cardiorespiratory effects of intravenous isoprenaline in mechanically ventilated dogs. *Br. J. Anaesth.*, **42**, 1042–1050.

FORDHAM, R. M. M. & RESNEKOV, L. (1968). Arterial hypoxaemia: a side effect of intravenous isoprenaline used after cardiac surgery. *Thorax*, **23**, 19–23.

FRITTS, H. W., HARRIS, P., CLAUSS, R. H., ODELL, J. E. & COURNAND, A. (1958). The effect of acetylcholine on the human pulmonary circulation under normal and hypoxic conditions. *J. clin. Invest.*, **37**, 99–110.

HAAS, F. & BERGOFSKY, E. H. (1968). Effect of pulmonary vasoconstriction on balance between alveolar ventilation and perfusion. *J. appl. Physiol.*, **24**, 491–497.

KELMAN, G. R. & NUNN, J. F. (1966). Nomograms for correction of blood PO_2, PCO_2, pH and base excess for time and temperature. *J. appl. Physiol.*, **21**, 1484–1490.

KELMAN, G. R., PALMER, K. N. V. & CROSS, M. R. (1969). Cardiovascular effects of AH3365 (Salbutamol). *Nature, Lond.*, **221**, 1251.

KENNEDY, M. C. S. & SIMPSON, W. T. (1969). Human pharmacological and clinical studies on Salbutamol: a specific β-adrenergic bronchodilator. *Br. J. Dis. Chest*, **63**, 165–174.

KNUDSON, R. J. & CONSTANTINE, H. P. (1967). An effect of isoproterenol on ventilation-perfusion in asthmatic versus normal subjects. *J. appl. Physiol.*, **22**, 402–406.

KRASNOW, N., ROLETT, E. L., YURCHAK, P. M., HOOD, W. B. & GORLIN, R. (1964). Isoproterenol and cardiovascular performance. *Am. J. Med.*, **37**, 514–525.

LOCKHART, A., EVEN, P., OURBAK, P., FERNANDEZ, F., ANGUERA, G., SCÉBAT, L. & LENÈGRE, J. (1966). Étude hémodynamique des blocs auriculo-ventriculaires chroniques acquis de l'homme. II. Effets de la stimulation asynchrone du ventricule doit et de la perfusion continue d'isopropylnoradrénaline. *Revue fr. Étud. clin. biol.*, **11**, 886–899.

LOCKHART, A., LISSAC, J., SALMON, D., ZAPPACOSTA, C. & BENISMAIL, M. (1967). Effects of isoproterenol on the pulmonary circulation in obstructive airways disease. *Clin. Sci.*, **32**, 177–187.

PALMER, K. N. V. & DIAMENT, M. L. (1967). Effect of aerosol isoprenaline on blood–gas tensions in severe bronchial asthma. *Lancet*, **2**, 1232–1233.

PALMER, K. N. V. & DIAMENT, M. L. (1969). Effect of salbutamol on spirometry and blood–gas tensions in bronchial asthma. *Br. med. J.*, **1**, 31–32.

PALMER, K. N. V., LEGGE, J. S., HAMILTON, W. F. D. & DIAMENT, M. L. (1970). Comparison of effect of salbutamol and isoprenaline on spirometry and blood–gas tensions in bronchial asthma. *Br. med. J.*, **2**, 23–24.

RIDING, W. D., DINDA, P. & CHATTERJEE, S. S. (1970). The bronchodilator and cardiac effects of five pressure-packed aerosols in asthma. *Br. J. Dis. Chest*, **64**, 37–44.

SPEIZER, F. E., DOLL, R. & HEAF, P. (1968). Observations on recent increase in mortality from asthma. *Br. med. J.*, **1**, 335–339.

SPEIZER, F. E., DOLL, R., HEAF, P. & STRANG, L. B. (1968). Investigation into use of drugs preceding death from asthma. *Br. med. J.*, **1**, 339–343.

SYKES, M. K. (1968). A mixing device for expired gas. *Anaesthesia*, **23**, 446–448.

SYKES, M. K. (1969). A pressure-operated collect valve for respiratory studies during intermittent positive pressure ventilation. *Br. J. Anaesth.*, **41**, 189–190.

TAI, E. & READ, J. (1967). Response of blood gas tensions to aminophylline and isoprenaline in patients with asthma. *Thorax*, **22**, 543–549.

WARRELL, D. A., ROBERTSON, D. G., HOWES, J. N., CONOLLY, M. E., PATTERSON, J. W., BEILIN, L. J. & DOLLERY, C. T. (1970). Comparison of cardiorespiratory effects of isoprenaline and salbutamol in patients with bronchial asthma. *Br. med. J.*, **1**, 65–70.

(*Received November* 2, 1970)