The African Journal of MEDICAL SCIENCES

Volume 4

1973

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Melbourne

Afr. J. med. Sci. (1973) **4**, 312–325.

Blood-gas Tension and Ventilatory Function in Asthmatics before and after Aerosol Isoproterenol

D. Femi-Pearse and Olufemi Elegbeleye

Lagos University Teaching Hospital, Private Mail Bag 12003, *Lagos, Nigeria.*

(*Received* 1 *December* 1972; *accepted* 12 *January* 1973)

Summary. Blood gas and ventilatory changes in sixteen asthmatics to the inhalation of Isoproterenol are described. Following inhalation of this drug, there were statistically significant rises in Pa_{O_2}, FEV_1, VC and PEFR. The average Pa_{CO_2} fell significantly. The most interesting observation in this study is the more consistent rise in Pa_{O_2} than that reported by other investigators among Europeans and Americans. The highly significant correlation between FEV_1 and PEFR emphasizes the usefulness of the latter in areas, where pulmonary function laboratories are non-existent. The FRC measured by the helium dilution method was highly variable. In this study, a rise or fall of FRC following inhalation of Isoproterenol was associated with a rise in Pa_{O_2} in most cases.

Résumé. Cette étude décrit l'échange du gaz et de la ventilation dans le sang due à l'inhalation de l'Isoproterenol parmi seize ásthmatiques. Après l'inhalation de ce médicament, il y a eu des élévations statistiquement importantes dans les Pa_{O_2} FEV_1, VC et PEFR le Pa_{CO_2} moyen est fortement tombé. L'observation la plus intèressante de cette étude a été l'augmentation dans le Pa_{O_2}, toujours plus élévé que celle reportée par d'autres chercheurs Européens et Américains. La correlation très remarquable entre FEV_1 et PEFR renforce l'utilité de ce dernier dans les regions où n'existent pas des laboratoires des fonctions pulmonaires. Le FRC mesuré par la métode de dilution de l'helium a été trés variable. Dans cette étude, une élévation ou une diminution de FRC après inhalation d'Isoproterenol a été associé, dans le plupart des cas, à une élévation de Pa_{O_2}.

INTRODUCTION

The pathophysiological characteristics of asthma are increased airway resistance and uneven distribution of ventilation. The effect on blood gases is hypoxaemia and hypocapnia (Waddell, Emerson & Gunstone, 1967; Palmer & Diament, 1967; Field, 1967; Tai & Read, 1967; McFadden & Lyons, 1968; Valabhji, 1968; Weng & Levison, 1969; Weng, *et al.*,

Correspondence: Professor D. Femi-Pearse, Lagos University Teaching Hospital, Private Mail Bag 12003, Lagos, Nigeria.

1970). While hypocapnia is the usual finding in most asthmatics, hypercapnia is a feature of severe or terminal asthma (Palmer & Diament, 1967; McFadden & Lyons, 1968).

Bronchodilator aerosols, containing Isoproterenol, which are used by a great number of asthmatics, confer significant subjective improvement and also produce objective changes especially in the forced vital capacity (FVC_1). Since airway resistance is reduced following aerosol Isoproterenol, the distribution of ventilation in asthmatics would be expected to improve with diminution of the degree of hypoxaemia. The converse of this concept is the observation of Raine & Bishop (1964) that inhalation of carbachol, a broncho-constrictor drug, reduces arterial oxygen tension ($Pa\text{O}_2$) and increases alveolar–arterial difference in oxygen tension, A*a* Po_2. Waddell *et al.* (1967) reported some improvement in $Pa\text{O}_2$ following inhalation of Isoproterenol and Meisner & Hugh-Jones (1968) showed increases in $Pa\text{O}_2$ after aerosol Orciprenaline. Some reports, however, show a worsening of hypoxaemia in asthmatics after aerosol Isoproterenol. This change has been attributed to increased ventilation–perfusion inequality. (Tai & Read, 1967; Knudson & Constantine, 1967; Palmer *et al.*, 1969).

In the course of studies on Nigerian asthmatics, a rise in arterial oxygen tension following inhalation of Isoproterenol was observed in most of them. Also, the lung volumes and dead-space/tidal volume (VD/VT) ratios were determined before and after inhalation of the drug. The results of these investigations form the basis of this report.

MATERIALS AND METHODS

Sixteen asthmatics—nine males and seven females—who were not severely breathless and could co-operate, had their static and dynamic lung volumes measured before and after inhalation of 1% Isoproterenol (Neo-epinine 1) (Burroughs Wellcome). The subjects were forbidden from taking broncho-dilator drugs at breakfast on the test day.

The procedure was as follows:

The FRC was determined in the sitting position by the method of Meenely & Kaltreider (1949) followed by the determinations of ERV and VC. A 6 l Spirometer* which had been calibrated by water displacement was used. The dynamic lung volumes were then measured in the standing position—FEV_1 and FVC with a Vitalograph† and PEFR with a Wright Peak Flow Meter. The subject now lay supine and Cournand's arterial needle was inserted into the brachial or femoral artery. A period of 5 min rest was allowed after which blood was drawn anaerobically and expired air was collected for 1 min. Blood gases ($Pa\text{O}_2$, $Pa\text{CO}_2$) and pH were measured by Instrumentation Laboratory blood gas analyser S113 already calibrated with known gas mixtures.

The CO_2 in expired air was assayed by Scholander micro-analysis. Dead-space/tidal volume ratio (VD/VT) was calculated from the Bohr equation. While still in the supine position the subjects inhaled 1% Isoproterenol for 3 min from a Collison inhaler employing compressed air at a flow rate of 10 l/min as a propellant. Fifteen minutes after the inhalation of Isoproterenol, blood was again drawn anaerobically for the estimation of blood gases and pH, and expired air was collected for 1 min for the determination of $Pa\text{CO}_2$, and VD/VT ratio. The subject now assumed the sitting position again for the measurement of FRC, ERV and VC; and in the standing position for FEV_1, FVC and PEFR. The whole procedure

* C. F. Palmer Recording Spirometer, C. F. Palmer, London.

† Vitalograph Clinical Outfit, Vitalograph Limited, Buckingham, England.

was completed within the hour. Finally, measurements of the static and dynamic lung volumes were repeated in the sitting and standing positions respectively.

Height and weight were measured without shoes and in light clothing. The better of two measurements each for ERV, VC, FEV_1 and FVC was recorded in this study. All lung volumes were corrected to body temperature and pressure saturated with water vapour at body temperature (BTPS), the exceptions being FEV_1 and FVC measured on the Vitalograph and recorded at ambient temperature and pressure (ATPS). Duplicate determinations were made on blood gases and the mean of the results recorded. The variations between duplicate determinations did not exceed 2 mm Hg for Pa_{O_2} and Pa_{CO_2}, and 0·005 units for pH in any subject.

Statistical comparisions, using the method of paired analysis, were made between the pre- and post-Isoproterenol values of all the variables. The IBM 1620 electronic data processing machine was used to develop a product moment correlation (r) matrix based on the variables measured.

RESULTS

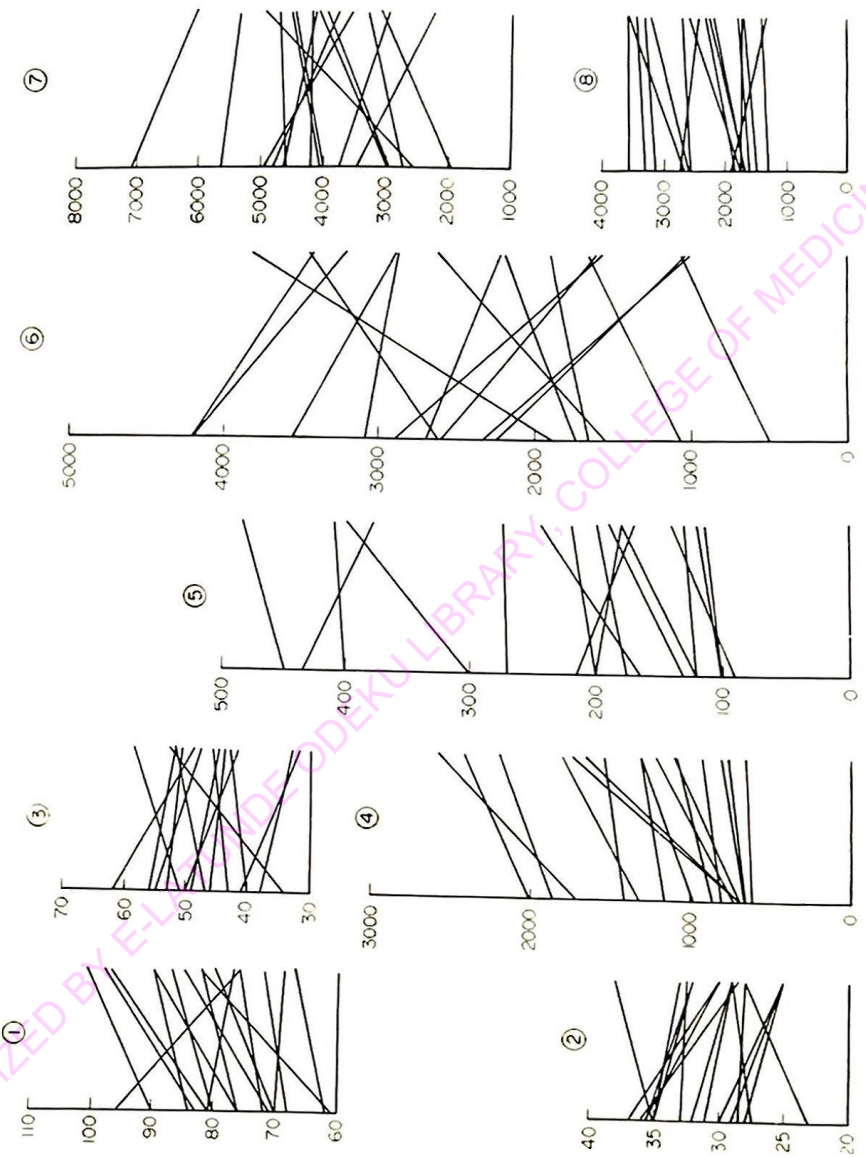
The mean values of the variables with complete data in sixteen subjects are shown in Table 1.

TABLE 1. Mean values and standard deviations of physical characteristics and pulmonary function values in sixteen asthmatics

	Before Isoproterenol		After Isoproterenol	
	Value	SD	Value	SD
VC (ml)	2386	871	2636†	908
FRC (ml)	2433	1001	2298^{NS}	908
ERV	785	443	825^{NS}	399
RV	1648	814	1473^{NS}	920
TLC	4035	1251	4110^{NS}	925
FEV_1	1041	455	1441‡	572
FVC	1920	534	2402‡	704
FEV_1 (%)	52·7	14·2	60·4‡	17·1
PEFR (l/min)	216·8	117·2	240*	113
Pa_{O_2}	76·3	9·2	82·9†	9·9
Pa_{CO_2}	31·9	3·8	29·6†	3·3
pH	7·436	0·032	$7·444^{NS}$	0·046
VD/VT	47·5	7·5	$46·3^{NS}$	7·2

* $P < 0·02$.
† $P < 0·01$
‡ $P < 0·001$.
NS Not significant.

In most of the subjects, the initial Pa_{O_2} was below normal. There were significant changes following inhalation of Isoproterenol in the following parameters: Pa_{O_2}; Pa_{CO_2}; FEV_1; PEFR; and VC. The changes in VD/VT, FRC, ERV, RV, TLC and pH did not reach significant levels. (Figs. 1–8). In nine out of fourteen patients in whom VD/VT was measured, the values fell with aerosol Isoproterenol. In the remaining five there was an increase (Fig. 3). Table 2 shows the correlation coefficients between FEV_1, PEFR and Pa_{O_2}.



FIGS. 1–8. Changes before and after inhalation of aerosol Isoproterenol. (1) Pao_2 (mmHg) $P<0{\cdot}01$; (2) $Paco_2$ (mmHg) $P<0{\cdot}01$; (3) VD/VT (%) not significant; (4) FEV_1 (ml) $P<0{\cdot}001$; (5) PEFR (l/min) $P<0{\cdot}02$; (6) FRC (ml) Helium dilution method, not significant; (7) TLC (ml) not significant; (8) VC (ml) $P<0{\cdot}001$.

TABLE 2. Correlation coefficients between FEV_1 and other measurements

Measurements	FEV_1 (ml)	PEFR (l/min)	Pa_{O_2} (mmHg)
Pre-Isoproterenol			
FEV_1	1·0	0·823‡	0·634†
PEFR	0·823‡	1·0	0·534*
Post-Isoproterenol			
FEV_1	1·0	0·852‡	0·417
PEFR	0·852‡	1·0	0·251

* $P<0·05$.
† $P<0·01$.
‡ $P<0·001$.

DISCUSSION

The results of this study accord with those of other authors that mild and moderate asthmatics have reduced arterial oxygen tensions (Waddell *et al.*, 1967; Palmer & Diament. 1967; Tai & Read, 1967; Weng *et al.*, 1970).

However, the results in this study differ from those of other investigators (Palmer & Diament, 1967; Field, 1967; Knudson & Constantine, 1967), who had significant diminution of Pa_{O_2} after inhalation of Isoproterenol, despite a significant increase in FEV_1 (Fig. 1). Raine & Bishop (1964) demonstrated a fall in Pa_{O_2} and an increase in alveolar–arterial difference in oxygen tension ($Aa\ P_{O_2}$) in normal subjects following aerosol administration of Carbachol, a parasympathomimetic drug. If aerosol carbachol causes increased airway resistance in normal subjects and a widened AaP_{O_2}, as a result of uneven distribution of inspired gas, then it might be expected that aerosol Isoproterenol would reduce airway resistance and improve arterial oxygen tension.

In thirteen out of sixteen patients Pa_{O_2} rose with aerosol Isoproterenol, while in two patients Pa_{O_2} showed moderate fall (Fig. 1). Apart from its powerful bronchodilator effect, Isoproterenol also produces substantial pulmonary vasodilatation through systemic absorption. Furthermore, as a result of its positive inotropic and chronotropic effects on the heart, cardiac output, and therefore pulmonary blood flow are increased. The Pa_{O_2} level after aerosol Isoproterenol would thus depend on the net effect of these pharmacological actions. There are, therefore, three possible directions of arterial oxygen tension change following aerosol Isoproterenol, viz: (1) Pa_{O_2} rise; (2) no change; and (3) fall of Pa_{O_2}. Tai & Read (1967) have documented these three responses.

The fall in Pa_{CO_2} and the concomitant rise in Pa_{O_2} following Isoproterenol in most of our patients would indicate improved alveolar ventilation and gas exchange (Fig. 2). The increased ventilation was probably distributed to alveoli which were previously underventilated with respect to their blood flow. The low Pa_{CO_2} values in this study also indicate that alveolar hypoventilation is not the cause of hypoxaemia in asthmatics. The hypocapnia in our asthmatics increased slightly with aerosol Isoproterenol. This was also the finding of McFadden & Lyons (1968).

The VD/VT ratios for individual patients were high before and after Isoproterenol—indicating ventilation/perfusion inequality (Waddell *et al.*, 1967; Field, 1967). In this study the mean VD/VT was virtually the same before and after Isoproterenol (47·5 and 46·3% respectively).

Several investigators found correlations between Pa_{O_2} and the flow measurements normally influenced by airway obstruction (Tai & Read, 1967; McFadden & Lyons, 1968; Weng *et al.*, 1970). In this study, FEV_1 and PEFR showed consistent improvement with aerosol Isoproterenol (Table 1). Moreover, before the administration of Isoproterenol, these measurements showed highly significant correlations with each other and with Pa_{O_2} (Table 2). It is clear, therefore, that for monitoring asthmatics PEFR could be a useful guide of airway obstruction in routine clinical practice, especially in Africa, where Pulmonary Laboratories are rare.

Meisner & Hugh-Jones (1968) found lower values for FRC and TLC in asthmatics, while employing the helium dilution method, as compared to the values obtained from the body plethysmograph. As in this study they also used an equilibration time of 5–7 min, whereas Woolcock & Read (1966) maintained equilibration time up to 20 min and recorded very high FRC and TLC in asthmatics. Three patterns of FRC change occurred in our patients—using the gas dilution method: (1) High initial FRC which fell with Isoproterenol; (2) low or normal initial FFC with a substantial rise following aerosol Isoproterenol; and (3) low or normal FRC showing no change with Isoproterenol (Fig. 6). The first pattern is the usual response. (Woolcock & Read, 1966; Weng & Levison, 1969). The second pattern would suggest that the pre-Isoproterenol FRC measurement was falsely low. With a gas dilution method for determining FRC, only the volume of lung being ventilated would be measured; all lung units not ventilated would be excluded from measurement. The FRC is, therefore, a highly variable parameter in asthmatics and would vary from time to time according to the number of ventilated lung units, when measured by a gas dilution method. Meisner & Hugh-Jones (1968) have, therefore, inferred that the under-estimate of the FRC by the helium dilution method would provide an assessment of the extent of under-ventilated lung units in asthmatics. Generally, the direction of change in FRC after Isoproterenol determined the values of TLC Moreover, a rise or fall of FRC following inhalation of Isoproterenol was associated with a rise of Pa_{O_2} in most patients.

ACKNOWLEDGMENTS

We thank Dr M. Doherty-Akinkugbe for selecting the patients; Mrs A. B. Oke, M.S., of the Institute of Computer Sciences, University of Lagos, for statistical analysis; Mr E. O. Omo-Osho and Mr P. T. Lawrence for blood–gas measurements and Mr S. N. C. Nwangwu for secretarial help.

REFERENCES

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.

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

MCFADDEN, E.R., JR, & LYONS, H.A. (1968) Arterial blood gas tensions in asthma. *New Engl. J. Med.* **278**, 1027.

MEENELY, C.R. & KALTREIDER, N.L. (1949) The volume of the lung determined by helium dilution. *J. clin. Invest.* **28,** 129.

MEISNER, P. & HUGH-JONES, P. (1968) Pulmonary function in bronchial asthma. *Brit. med. J.* **1,** 470.

PALMER, K.N.V. & DIAMENT, M.L. (1967) Spirometry and blood gas tensions in bronchial asthma and chronic bronchitis. *Lancet*, **ii,** 383.

PALMER, K.N.V., LEGGE, J.S., HAMILTON, W.F.D. & DIAMENT, M.L. (1969) Effect of a selective Beta-adrenergic blocker in preventing falls in arterial oxygen tension following Isoproterenol in asthmatic subjects. *Lancet*, **ii,** 1092.

RAINE, J.M. & BISHOP, J. (1964) Alterations in ventilation–perfusion relationships in the lung after breathing inert dust or broncho-constrictor aerosols and after short periods of voluntary hyperventilation. *J. clin. Invest.* **43,** 557.

TAI, E. & READ, J. (1967) Response of blood gas tension to Aminophylline and Isoproterenol in patients with asthma. *Thorax*, **22,** 543.

VALABHJI, P. (1968) Gas exchange in the acute and asymptomatic phases of asthma breathing air and oxygen. *Clin. Sci.* **34,** 431.

WADDELL, J.A., EMERSON, P.A. & GUNSTONE, R.F. (1967) Hypoxia in bronchial asthma. *Brit. med. J.* **2,** 402.

WENG, T., LANGER, H. M., FEATHERBY, E.A. & LEVISON, H. (1970) Arterial blood gas tensions and acid–base balance in symptomatic and asymptomatic asthma in childhood. *Amer. Rev. resp. Dis.* **101,** 274.

WENG, T. & LEVISON, H. (1969) Pulmonary function in children with asthma at acute attack and symptom-free status. *Amer. Rev. resp. Dis.* **99,** 719.

WOOLCOCK, A.J. & READ, J. (1966) Lung volumes in exacerbations of asthma. *Amer. J. Med.* **4,** 259.