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Effects of verapamil on pulmonary haemodynamics during hypoxaemia, at rest, and during exercise in patients with chronic obstructive pulmonary disease

STEPHEN E BROWN, GREGORY S LINDEN, RANDEL R KING, GREGORY P BLAIR, DAVID W STANSBURY, RICHARD W LIGHT

From the Medical Service, Veterans Administration Medical Center, Long Beach, California, and the University of California, Irvine, USA

ABSTRACT The haemodynamic effects of intravenous verapamil at rest, during hypoxaemia, and during progressive exercise were evaluated in 10 patients with chronic obstructive lung disease. Verapamil produced significant decreases in the peak heart rate and systemic blood pressure during exercise but exercise capacity and pulmonary gas exchange at exhaustion were unaffected. There were no significant changes in pulmonary artery pressure or total pulmonary vascular resistance during exercise or during the breathing of either air or a hypoxic gas mixture at rest. No clinically useful benefit was found with verapamil in the dosage used in this group of patients and the value of calcium antagonists in the treatment of patients with chronic obstructive lung disease requires further clarification.

Calcium antagonists may be effective in lowering pulmonary artery pressures in patients with chronic obstructive lung disease. Verapamil has been shown to inhibit calcium induced contraction of rabbit pulmonary artery strips in vitro[1] and to attenuate the hypoxic pulmonary pressor response in laboratory animals.[2–4] Small decreases in pulmonary artery pressure with the drug have been reported in human subjects with pulmonary hypertension.[5] The current study was undertaken to elucidate further the effects of verapamil in patients with chronic obstructive lung disease.

Methods

Study population Ten patients aged 35–75 years who had a one second forced expiratory volume (FEV_1) of 1·5 l or less and FEV_1/forced vital capacity (FVC) of 55% or less, and who were in a stable state, were studied (table 1). Patients with both chronic bronchitis and emphysema were included. Patients with known left ventricular disease and those taking beta adrenergic blocking agents, antiarrhythmics, or digitalis were excluded. All patients were taking long acting theophylline compounds and nebulised metaproterenol. These agents were last administered about one hour before the study began.

Study protocol Catheters were placed in the radial and pulmonary arteries. Mean pulmonary artery pressure ($\overline{PAP}$) was measured with patients seated breathing room air and the measurements were repeated while they breathed a hypoxic gas mixture.

Table 1 *Age and pulmonary function in the 10 patients studied*

	Mean (SD)	*Range*
Age (y)	61 (13)	49–72
FEV_1 (l)	0·89 (0·29)	0·4–1·50
FVC (l)	2·21 (0·60)	1·6–3·6
FEV_1/FVC (%)	40·9 (8·5)	28–55
T_{LCO} (% predicted)	43·7 (19·8)	14–92
TLC (% predicted)	146 (28)	98–201
FRC (% predicted)	257 (49)	182–341
RV (% predicted)	347 (67)	251–456
sGaw (s^{-1} cmH_2O^{-1})	0·06 (0·03)	0·03–0·13

FVC—forced vital capacity; T_{LCO}—diffusing capacity (transfer factor); TLC—total lung capacity; FRC—functional residual capacity; RV—residual volume; sGaw—specific conductance (conversion to $s^{-1}kPa^{-1} \times 10$).

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Address for reprint requests: Dr SE Brown, Medical Center, Veterans Administration, 5901 East Seventh Street, Long Beach, California 90822, USA.

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An exercise test was then performed, followed by a 45 minute rest. Verapamil (supplied by Knoll Pharmaceutical Company) was administered intravenously (0·1 mg/kg bolus, followed by a 0·005 mg/kg/min infusion). Five minutes after the verapamil bolus PAP was measured while the patients were resting seated and breathing room air and the entire study sequence outlined above was repeated within 60 minutes during verapamil infusion. Intravascular pressures were measured with Statham P 23 ID pressure transducers. Transducer positions were carefully marked for ensuring reproducibility of measurements.

Hypoxic measurements The patient was seated with noseclip in place and breathing through a Hans-Rudolph valve; an ear oximeter (Hewlett-Packard 47201A) was used to monitor the arterial oxygen saturation (Sao_2). After a five minute period of stabilisation, PAP, mean systemic pressure (BP), and Sao_2 were measured. Then with continous cardiac and Sao_2 monitoring the oxygen concentration of the inspired gas mixture (FiO_2) was decreased to between 0·13 and 0·15 by blending nitrogen with room air to decrease the Sao_2 by at least 10%. When the desired hypoxic Sao_2 was reached, simultaneous measurements of $\overline{PAP}$, $\overline{BP}$, and Sao_2 were repeated and the patient was then returned to breathing room air. An identical procedure using the same hypoxic FiO_2 was repeated during verapamil infusion. Hypoxic Sao_2 did not differ in the control and verapamil studies (77·0% (SEM 4·1%) and 76·2% (3·9%) respectively); in individual patients the % Sao_2 varied by no more than 1·5 between the two studies.

Resting measurements With the patient seated on a cycle ergometer $\overline{PAP}$, $\overline{BP}$, arterial and mixed venous blood gases, Sao_2 and $S\bar{v}o_2$, heart rate, respiratory rate, and cardiac output ($\dot{Q}$, on the basis of the Fick equation) were measured. Total pulmonary vascular resistance (TPR = PAP/Q, mm Hg $l^{-1}min^{-1}$), and total systemic vascular resistance (TSR = BP/Q, mm Hg $l^{-1}min^{-1}$) were obtained.

Exercise measurements Progressive exercise testing was performed to exhaustion with work loads increasing by 15–25 w every four minutes. Haemodynamic, expired gas, and blood gas measurements were obtained during the last minute at each work load. Mixed expired gas was analysed for fractional expired carbon dioxide and oxygen ($FeCO_2$ and Feo_2) (Beckman LB-2 and OM-11); expired volume was measured in a Tissot 120 l gasometer. Metabolic values were obtained from standard equations.[6]

Each patient gave his informed written consent. Data were analysed with Student's paired *t* test and linear regression by the least squares technique.

Results

Hypoxic data With the decrease in Fio_2, Sao_2 decreased from 91·3% (SD 3·8%) to 77·0% (4·1%) before verapamil infusion and similarly from 90·9% (3·7%) to 76·2% (3·9%) during the infusion. Measurements of $\overline{PAP}$ are shown in figure 1. The slight increase in $\overline{PAP}$ while subjects were breathing room air and the slight decrease in PAP while they were breathing the hypoxic mixture after verapamil were not significant.

Resting data Haemodynamic and gas exchange data are summarised in figure 2 and table 2. There were no significant changes after the verapamil infusion apart from a slight increase in the dead space: tidal volume ratio (VD/VT).

Exercise data The data obtained during exercise are summarised in figure 2 and table 3. There were no significant changes for the group as a whole in $\overline{PAP}$ or TPR during maximal exercise. The BP and heart rate at exhaustion decreased significantly with verapamil. Exercise tolerance was not affected. There was substantial variation between individuals

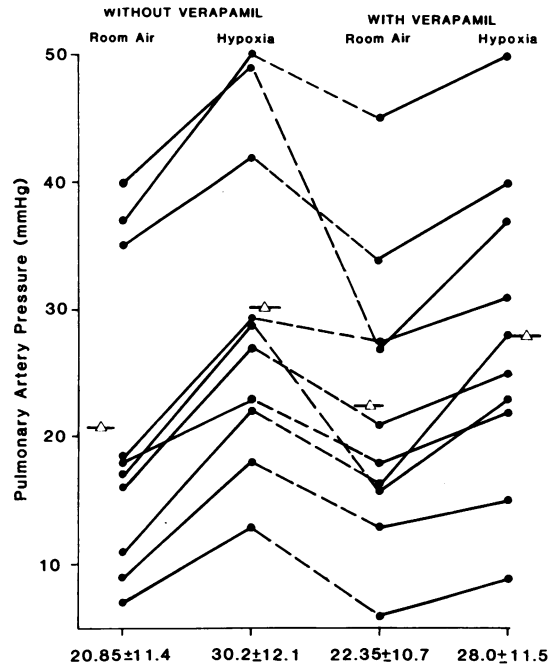

Fig 1 *Pulmonary artery pressure during normoxia and hypoxia with and without verapamil. Closed circles connected by solid lines denote individual patients. Mean and SD values are shown below the illustration and also depicted by open triangles. Broken lines allow comparison of the responses of individual patients to verapamil.*

Table 2 *Haemodynamic data (mean (SD) values) obtained at rest with and without verapamil*

	Control	*Verapamil*
Mean systemic blood pressure (mm Hg)	106 (17)	99 (14)
Mean pulmonary artery pressure (mm Hg)	18·6 (8·8)	21·6 (11·8)
Heart rate (beats/min)	94 (17)	90 (16)
Cardiac output (l min^{-1})	4·49 (0·68)	4·72 (0·80)
Total pulmonary vascular resistance (units)	4·5 (1·7)	4·9 (2·9)
Total systemic vascular resistance (units)	24·2 (4·8)	21·8 (5·0)
Arterial oxygen tension (mm Hg)	72 (12)	70 (13)
Mixed venous oxygen tension (mm Hg)	31 (2)	32 (3)
Arterial carbon dioxide tension (mm Hg)	41 (6)	41 (6)
Alveolar-arterial oxygen tension difference (mm Hg)	31 (10)	34 (12)
Deadspace fraction (V_D/V_T)	0·51 (0·06)	0·54 (0·06)*
Oxygen consumption (l min^{-1})	0·30 (0·05)	0·30 (0·05)

*$p < 0.02$
Conversion: Traditional to SI units—Arterial pressure and blood gas tension: 1 mm Hg = 0·133 kPa.

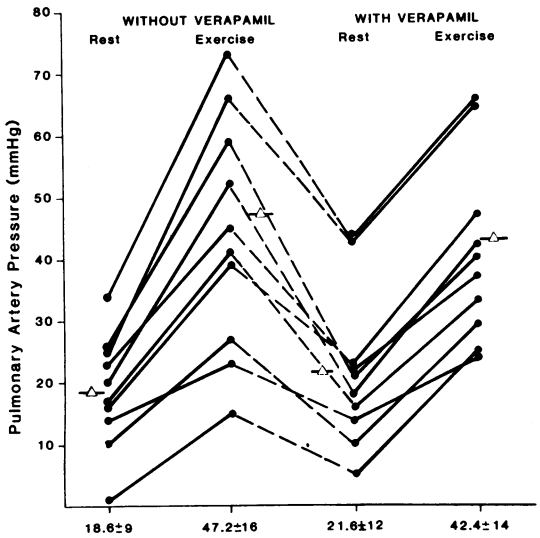

Fig 2 *Pulmonary artery pressure at rest and during exercise with and without verapamil (see fig 1 for symbols).*

in the pulmonary haemodynamic response to the drug, with increases in $\overline{PAP}$ and TPR in some patients and decreases in others. The effects of verapamil were also examined during exercise at the highest submaximal work level and again there were no significant changes from control values (table 4). Data on individual patients relating to tables 3 and 4 are available from the authors on request.

Discussion

Verapamil has been shown to produce decreases in hypoxic pulmonary artery pressures in laboratory [1][9] but we were unable to show such beneficial effects during the stress of hypoxia in our human subjects with chronic obstructive lung disease. Neither did we find any consistent effects on pulmonary haemodynamics during exercise, but considerable inter-individual variability in the response to verapamil was seen.

Our resting data on patients with chronic obstructive lung disease are similar to those of Ferlinz *et al*[10] and Singh and Roche,[11] who showed small increases in pulmonary artery pressure with verapamil in patients with cardiac disease. In the former study the dose of intravenous verapamil was identical to that in our study; in the latter study a single 10 mg intravenous dose was administered. In contrast,

Table 3 *Haemodynamic data (mean (SD) values) obtained during maximal exercise with and without verapamil*

	Control	*Verapamil*
Mean systemic blood pressure (mm Hg)	136 (23)	120 (22)**
Mean pulmonary artery pressure (mm Hg)	43 (18)	40 (13)
Heart rate (beats/min)	125 (15)	117 (14)*
Cardiac output (l min^{-1})	8·04 (1·7)	7·72 (2·1)
Total pulmonary vascular resistance (units)	5·5 (2·6)	5·6 (2·7)
Total systemic vascular resistance (units)	17·2 (5·0)	16·8 (5·2)
Arterial oxygen tension (mm Hg)	70 (16)	69 (15)
Mixed venous oxygen tension (mm Hg)	27 (4)	26 (4)
Arterial carbon dioxide tension (mm Hg)	45 (8)	43 (8)
Alveolar-arterial oxygen tension difference (mm Hg)	34 (11)	34 (12)
Deadspace fraction (V_D/V_T)	0·45 (0·09)	0·47 (0·08)
Oxygen consumption (l min^{-1})	0·82 (0·23)	0·79 (0·23)

*$p < 0.05$; **$p < 0.001$.
Conversion: Traditional to SI units—Arterial pressure and blood gas tension: 1 mm Hg = 0·133 kPa.

Table 4 *Haemodynamic data (mean (SD) values) obtained during submaximal exercise*

	Control	*Verapamil*	*p*
Mean systemic blood pressure (mm Hg)	123 (23)	115 (18)	NS
Mean pulmonary artery pressure (mm Hg)	36·2 (15·0)	35·9 (13·0)	NS
Heart rate (beats/min)	119 (17)	110 (14)	<0·025
Cardiac output (l min^{-1})	8·36 (2·10)	8·69 (2·30)	NS
Total pulmonary vascular resistance (units)	4·48 (1·70)	4·32 (1·60)	NS
Total systemic vascular resistance (units)	15·9 (4·90)	14·6 (5·3)	NS
Oxygen consumption (l min^{-1})	0·74 (0·22)	0·73 (0·25)	NS

Conversion: Traditional to SI units—Arterial pressure: 1 mm Hg = 0·133 kPa.

Landmark *et al*[5] reported a decrease in mean resting pulmonary artery pressure in patients with pulmonary hypertension after an injection of verapamil (0·15 mg/kg) into the pulmonary artery. Verapamil has failed to alter total pulmonary vascular resistance in other studies[10 11] but one preliminary report indicated a decrease in TPR in patients with hypoxic lung disease.[12] Landmark *et al*[5] noted appreciable variation between individuals in the pulmonary haemodynamic response to verapamil.

In calculating the vascular resistances in this study we did not subtract the central venous pressure and the pulmonary artery wedge pressure since they were not available during exercise. It is possible that either of these pressures might have changed after verapamil administration, but we doubt that this would have altered our conclusions. Very low mean pulmonary artery pressures were recorded in one or two patients. The pulmonary artery catheters were inserted while the patients were supine and measurements were recorded for the study while the patients were in the sitting position. The catheter tip in these patients was probably closer to the lung apex, causing pressure measurements in the seated posture to be low. The resting cardiac outputs in our group of patients may appear to be somewhat low. The likely explanation for this is that the cardiac output decreases with a change from the supine to the upright posture and reference values are usually measured in the supine position.

That verapamil did not alter maximum exercise performance in our patients is not surprising, since they were probably impeded primarily by limitations of their ventilatory mechanics rather than pulmonary haemodynamics. We are not aware of any previous reports which have examined the effects of verapamil during exercise in patients with chronic obstructive lung disease. Atterhog and Ekelund[13] showed an increase in pulmonary vascular resistance during exercise with no change in exercise pulmonary artery pressures in healthy middle aged subjects. A recent report describes improved pulmonary haemodynamics during rest and exercise with diltiazem in a small group of patients with pulmonary hypertension.[14]

Since there was considerable variation between individuals in the haemodynamic response to verapamil we attempted to identify distinguishing characteristics of those patients who may have benefited from the drug. Three patients had a lower mean pulmonary artery pressure with verapamil in each condition studied. This group of "consistent improvers" had a greater diffusing capacity than the remainder of the group ($p < 0.05$, Student's unpaired t test); but no other clinical characteristics or other measurements of pulmonary function identified responders, so this distinction is of doubtful importance.

This study failed to show any significant pulmonary haemodynamic effects from verapamil in the dosage used. Whether larger doses of the drug or different criteria for selecting patients would result in significant pulmonary haemodynamic effects is not known. More beneficial pulmonary haemodynamic effects may be seen with the calcium antagonists nifedipine and diltiazem,[14 18 19] both of which have less cardiac effect than verapamil; but the role (if any) of the calcium antagonists in the treatment of chronic obstructive lung disease remains to be defined.

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