Haemodynamic effects of phentolamine in chronic obstructive pulmonary disease

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Ten patients with chronic obstructive pulmonary disease without complicating cor pulmonale were studied by right and left heart catheterization. Respiratory and haemodynamic observations were made during a control period and during the infusion of phentolamine. Phentolamine produced a significant reduction in mean pulmonary artery pressure from 18.8 mmHg to 13.1 mmHg, right ventricular end-diastolic pressure from 1.8 mmHg to 0.1 mmHg, and left ventricular end-diastolic pressure from 8.2 mmHg to 1.9 mmHg. The mean brachial artery pressure, cardiac index, and pulmonary vascular resistance were essentially unchanged. It is concluded that the haemodynamic response of the patients to phentolamine cannot be explained by a single mechanism. Multiple actions of the drug must be considered, including active pulmonary vasodilatation, and a positive inotropic action upon the heart.

The administration of phentolamine at an infusion rate of 0.3 mg/min to patients in congestive heart failure produces a striking haemodynamic improvement. The cardiac output, cardiac rate, systemic pressure, and stroke index increase while the pulmonary artery pressure, systemic peripheral resistance, left ventricular end-diastolic pressure, and left ventricular end-diastolic volume fall (Gould, Zahir, and Ettinger, 1969). Further, this conspicuous improvement of cardiac dynamics occurs within minutes, and is not associated with any untoward side effects.

Taylor *et al.* (1965a) studied the pulmonary circulation in normal and hypertensive patients before and after the acute intravenous injection of 5 mg phentolamine. The drug caused a prompt reduction in the right atrial, pulmonary arterial, systemic arterial, and wedge pressures. The cardiac output was invariably increased while the pulmonary vascular resistance was decreased. They concluded that the predominant vascular activity of the drug was to cause a direct relaxation of the vascular smooth muscle, affecting not only the systemic resistance vessels but also the pulmonary and systemic venous circulation.

Phentolamine has an antispasmodic action in the isolated guinea-pig lung (Wiśniewska, 1964). In addition, it has recently been shown

that a significant improvement in pulmonary function tests occurs in normal man, as well as in patients with pulmonary emphysema, when a nebulizer containing 5 mg phentolamine in 1 ml water is used (Gould and Dilieto, 1970).

These observations led us to consider the use of phentolamine in chronic pulmonary disease. We now report the effects of an intravenous infusion of phentolamine in patients with chronic obstructive pulmonary disease without cor pulmonale.

Patients and method

Ten patients with chronic bronchitis or obstructive pulmonary emphysema, or both, without complicating cor pulmonale were studied. All patients had normal heart size on radiological examination and normal electrocardiograms. There was no clinical evidence of coronary or valvular heart disease and none had diastolic hypertension. Their physical characteristics and pulmonary function tests are shown in Table 1. All patients were able to lie supine with one pillow for the 2½-hour study period, and none was in acute respiratory distress. Studies were performed in the fasting, post-absorptive state without premedication.

Catheterization of the left ventricle was performed by retrograde arterial catheterization through a brachial arteriotomy. A Courmand needle was placed into the opposite brachial artery. To ensure high fidelity tracings, the needle was directly connected to a Statham pressure transducer, model P23Db. A No. 7 Goodale

TABLE I Pulmonary function studies in 10 patients with chronic obstructive pulmonary disease

Case No.	Sex	Age (yr)	Body surface area	Vital capacity (ml)		FEV _{1.0}		MVV (l./min)	
				Control	Phen	Control	Phen	Control	Phen
1	F	38	1.56	2730 (2970)	2570	12 (83)	9	48 (83)	34
2	M	60	1.86	3700 (4380)		51 (83)		55 (79)	
3	M	50	1.75	2620 (3740)	2580	38 (83)	32	41 (100)	41
4	F	32	1.70	1360 (3410)	1420	38 (83)	40	16 (90)	22
5	M	72	1.68	2920 (3440)	3100	32 (83)	28	37 (77)	35
6	M	62	1.56	2760 (3740)		52 (83)		48 (67)	
7	M	62	1.60	2325 (3400)	2510	18 (83)	22	19 (91)	26
8	M	70	1.73	2820 (3400)		55 (83)		24 (83)	
9	M	21	1.78	4660 (4620)		26 (83)		74 (136)	
10	F	25	1.72	4280 (3500)		53 (83)		66 (103)	

FEV_{1.0} = forced expiratory volume - 1 second; MVV = maximum voluntary ventilation (BTPS); figures in parenthesis indicate predicted values.

Lubin catheter was placed in the pulmonary artery. Cardiac output was determined in duplicate by the Fick technique. Oxygen consumption was determined by measuring ventilation with a Tissot spirometer, and analysing the expired gas with a Micro-Scholander apparatus. Mixed venous blood was obtained from the pulmonary artery and arterial blood from the brachial artery. Arterial and mixed venous oxygen contents were determined by the method of Van Slyke and Neill. Arterial blood gases and pH were measured with the pH/gas analyser manufactured by Instrumentation Laboratories. Left ventricular, pulmonary arterial and systemic arterial pressures, and cardiac output were measured in the resting state. All pressures were obtained using the mid-thoracic level as the reference point.

Phentolamine was then infused intravenously at 0.3 mg/minute. Pressures and cardiac output were measured 15 minutes after the onset of the infusion.

Ventricular function was assessed according to the following parameters:

- (1) $LVS\dot{W} = LV_s - LV_d / 100 \times SI \times 1.36 \times 1.050$
- (2) $RVS\dot{W} = RV_s - RV_d / 100 \times SI \times 1.36 \times 1.050$
- (3) $TPR = BAm \times 1332 / CO$
- (4) $PVR = PAm - LV_d \times 1332 / CO$

Where $LVS\dot{W}$ = left ventricular stroke work (g m/beat per m² body surface area);

SI = stroke index (ml/beat per m² body surface area);

LV_s = mean left ventricular systolic pressure (mmHg);

LV_d = left ventricular end-diastolic pressure (mmHg);

$RVS\dot{W}$ = right ventricle stroke work (g m/beat per m² body surface area);

RV_s = mean right ventricular systolic pressure (mmHg);

RV_d = right ventricular end-diastolic pressure (mmHg);

TPR = total peripheral resistance (dynes - sec - cm⁻⁵);

BAm = mean brachial artery pressure (mmHg);

CO = cardiac output (ml/sec);

PVR = pulmonary vascular resistance (dynes - sec - cm⁻⁵);

PAm = mean pulmonary artery pressure (mmHg);

1.36 = conversion factor from mmHg to cm water;

1.050 = whole blood specific gravity.

The statistical significance of the differences (P values) between the control values and phentolamine values was calculated with the Student t test.

Five of the catheterized patients subsequently received phentolamine at an infusion rate of 0.3 mg/minute for 15 minutes. This was performed in order to measure the vital capacity, maximum voluntary ventilation, and the one second forced expiratory volume before and after phentolamine.

Results

Complete data on all 10 patients are presented in Table 2. A summary and statistical analysis of the various parameters during the control period and during the phentolamine infusion are included in this Table.

Observations at rest Four patients had pulmonary artery systolic pressures exceeding 30 mmHg. No patient had an abnormal increase in the right or left ventricular end-diastolic pressure. The cardiac index was within normal limits (2.5 to 3.5 l./min per m²) in 8 patients, low in 1, and high in 1. The partial pressure of carbon dioxide was above normal (46 mmHg) in 1 patient (Case 5), and the arterial oxygen saturation was below normal (92%) in 3 patients.

Phentolamine infusion The pulmonary artery systolic, diastolic, and mean pressures, the right ventricular end-diastolic pressure, and the left ventricular end-diastolic pressure fell in each patient. When the control values are compared to the values during the phentolamine infusion, the average pulmonary artery mean pressure decreased from 18.8 mmHg to 13.1 mmHg ($P < 0.01$). The average right ventricular systolic pressure fell from 29.6 to 19.7 mmHg ($P < 0.01$), while the average right ventricular end-diastolic pressure fell from 1.8 to 0.1 mmHg ($P < 0.02$). The average left ventricular end-diastolic pressure fell from 8.2 to 1.9 mmHg ($P < 0.001$). The brachial artery pressure showed no significant change. The intracardiac pressures were measured 60 minutes after the onset of the infusion and were comparable to the 15-minute values.

The cardiac index, stroke index, heart rate, oxygen consumption, and arteriovenous oxygen difference did not reveal any significant change during the phentolamine infusion.

The average calculated total peripheral resistance and pulmonary vascular resistance fell minimally during the infusion. The average left ventricular stroke work increased while the average right ventricular stroke work decreased during the infusion. The changes were not statistically significant.

During the administration of phentolamine the minute ventilation increased significantly from 5.34 to 6.66 l./min per m² ($P < 0.05$). There was no significant change in the arterial blood pH or in the average arterial oxygen saturation. The oxygen and carbon dioxide tension in arterial blood also showed minimal changes.

The pulmonary function studies showed little change after the administration of phentolamine.

Discussion

All the patients studied had clinical evidence of chronic obstructive pulmonary disease. The pulmonary function tests showed variable degrees of impairment though all the patients

showed moderate to severe impairment of the maximum voluntary ventilation.

All the patients studied had essentially normal haemodynamic findings before phentolamine administration, so that any directly measured changes produced by the drug must of necessity be small. Moreover, derived data suffer from compounding such small changes. During the infusion of phentolamine there was a significant reduction in the filling pressures of both ventricles and the mean pressures in the pulmonary artery. There was no appreciable change in the cardiac index or systemic arterial pressure. These haemodynamic changes can probably be explained by the recently described inotropic action of the drug.

The administration of 5 mg phentolamine intravenously to normal dogs, each with a strain gauge arch attached to the right ventricle, will increase the ventricular contractile force (Gould *et al.*, 1969). This positive inotropic response in animals has also been seen in humans by employing the left ventricular dp/dt (Gould *et al.*, 1969). This measurement is much increased after the administration of phentolamine. This improvement in cardiac function may be explained by the recent observations of Dairman *et al.* (1968). They administered phentolamine (5 mg/kg) to rats. At the height of alpha-receptor blockade, the conversion of a tracer dose of tyrosine-¹⁴C to norepinephrine in the heart, brain, and adrenal gland was increased threefold with no alteration in specific activity of tyrosine in blood and tissues. From these studies, Dairman concluded that receptor blockade led to increased synthesis and release of norepinephrine in three organs that were measured. Our studies with smaller doses of phentolamine have indicated a positive inotropic effect. In view of the findings of Dairman and his co-workers, it could reasonably be assumed that the inotropic effect results from increased production of catecholamines in the myocardium. This contention has received support from the recent work of Bagwell *et al.* (1970). They administered 5 mg/kg of phentolamine to 7 experimental animals and observed an increase in the left ventricular contractile force. If the animals were pretreated with reserpine, phentolamine's inotropic action could be blocked. A subsequent infusion of norepinephrine could then restore the positive inotropic effect of phentolamine. The authors concluded that the positive inotropic action of phentolamine was dependent on the release of norepinephrine.

Taylor *et al.* (1965a) administered 5 mg phentolamine intravenously to normal and

TABLE 2 Haemodynamic and respiratory responses to phentolamine

Case No.	Left ventric. stroke work g m/beat/m ²		Right ventric. stroke work g m/beat/m ²		Total periph. resist. (dynes sec cm ⁻⁵)		Pulm. vasc. resist. (dynes sec cm ⁻⁵)	
	Control	Phen	Control	Phen	Control	Phen	Control	Phen
1	55	66	9.0	7.9	2080	1585	99	63
2	34	62	8.2	7.2	1680	955	262	85
3	48	63	16.0	12	1450	1100	177	168
4	99	86	21.2	10.3	1920	2130	183	200
5	74	77	20.0	14.7	1630	1740	206	221
6	52	79	11.8	9.4	1350	1380	158	160
7	77	116	16.0	20	1720	1340	250	235
8	92	87	14.3	8.9	1650	1770	129	148
9	51	51	16	10.4	1250	1200	156	166
10	—	—	10.3	8.8	1020	1160	102	120
Mean	64.7	76.3	14.3	11.0	1575	1436	172.2	156.6
±SD	21.9	19.1	4.4	3.8	315.3	364.6	55.8	55.5
±SE	7.3	6.4	1.4	1.2	99.7	115.3	17.6	17.6
P value	NS		NS		NS		NS	

Case No.	Cardiac index (l./min/m ²)		Stroke index (ml/m ²)		Heart rate (beats/min)		O ₂ consumpt. (ml/min/m ²)		AV O ₂ diff. (vol %)	
	Control	Phen	Control	Phen	Control	Phen	Control	Phen	Control	Phen
1	2.57	3.22	35	37	75	88	111	132	4.3	4.1
2	1.96	3.64	23	36	84	100	94	109	4.8	3.0
3	2.84	3.81	32	38	88	100	128	140	4.5	3.7
4	2.83	2.56	45	36	63	72	138	131	4.9	5.1
5	3.02	2.85	40	38	75	75	157	159	5.2	5.6
6	3.24	3.18	33	44	100	71	171	159	5.3	5.0
7	3.00	3.81	40	54	75	79	141	172	4.7	4.5
8	3.32	3.11	37	31	88	100	175	161	5.4	5.2
9	3.16	3.24	34	33	94	97	158	158	5.0	4.9
10	4.10	3.88	38	41	107	94	184	163	4.1	3.9
Mean	3.00	3.33	35.7	38.8	84.90	87.60	145.1	148.4	4.8	4.5
±SD	0.55	0.44	5.9	6.5	13.30	12.21	28.9	19.55	0.43	0.81
±SE	0.17	0.14	1.9	2.0	4.21	3.86	9.13	6.18	0.14	0.26
P value	NS		NS		NS		NS		NS	

hypertensive patients and observed a rise in the cardiac index and a fall in the systemic arterial pressure. However, they also noted a reduction in the ventricular filling pressures and pulmonary artery pressures.

These varying results can be explained by the dose of phentolamine used in the two studies. The high dose of phentolamine produced predominant vasodilatation with a resultant obvious fall in the blood pressure. The decrease in the peripheral resistance led to a reflex increase in the cardiac output. The low dose of phentolamine (0.3 mg/min) that we employed in our study produced no change in the systemic pressure or peripheral resistance. This was due to the predominant inotropic effect of the drug which masked phentolamine's vasodilating action. The negligible change in the cardiac output may at first appear paradoxical. This response has, however, been explained by Braunwald, Ross, and Sonnenblick (1967). They state that the contractile state of the myocardium is not the

factor that limits the volume of blood ejected by the heart in the normal person, and that an improvement of myocardial contractility by a drug with a positive inotropic effect would not be expected to increase the output in a normal subject.

Phentolamine consistently lowers pressures in the pulmonary circulation, no matter what dose is employed (Gould *et al.*, 1969; Evans, Smulyan, and Eich, 1967; Taylor *et al.*, 1965b). This effect, often accompanied by a fall in the pulmonary vascular resistance, has been considered evidence suggestive of pulmonary vasodilatation. The pulmonary blood volume was not determined in the study. However, Taylor *et al.* (1965a) determined that the acute injection of phentolamine was followed by a fall in the pulmonary artery and left atrial pressures at a time when there was a considerable increase in pulmonary blood volume. They concluded that the drug caused a direct relaxation of the vascular smooth muscles of the pulmonary bed. This is the

TABLE 2 Continued

Case No.	S_aO_2 (%)		P_aCO_2 (mmHg)		P_aO_2 (mmHg)		pH		V_E (l./min/m ²)	
	Control	Phen	Control	Phen	Control	Phen	Control	Phen	Control	Phen
1	90	93	29	25	65	55	7.50	7.59	3.88	7.02
2	92	92	42	35	62	63	7.46	7.45	3.88	5.33
3	88	84	37	34	52	49	7.47	7.43	5.66	6.20
4	93	90	38	36	68	60	7.42	7.43	3.84	4.05
5	92	90	60	55	60	55	7.48	7.51	4.86	5.60
6	96	94	—	—	—	—	—	—	6.83	7.75
7	92	88	—	—	—	—	—	—	5.60	7.20
8	92	94	34	31	68	69	7.55	7.51	6.72	8.79
9	91	91	36	35	63	62	7.42	7.43	6.40	7.56
10	94	91	—	—	—	—	—	—	5.73	7.07
Mean	92	90.1	39.4	35.9	62.6	59	7.47	7.48	5.34	6.66
±SD	2.2	3.0	9.9	9.2	5.5	6.6	0.05	0.06	1.12	1.38
±SE	0.7	1.0	3.7	3.5	2.1	2.5	0.02	0.02	0.37	0.44
P value	NS		NS		NS		NS		<0.05	

Case No.	Brachial artery		Pressures (mmHg)						Pulmonary artery mean		Left ventricular			
			Right ventricular diastolic		systolic		systolic				diastolic			
	Control	Phen	Control	Phen	Control	Phen	Control	Phen	Control	Phen	Control	Phen		
1	130/88 (105)	140/80 (100)	4	0	22	15	15	10	120	130	10	6		
2	110/60 (77)	115/65 (81)	0	0	25	14	15	10	105	120	3	0		
3	120/75 (90)	125/75 (92)	0	0	35	22	21	14	115	115	10	0		
4	165/90 (115)	170/90 (117)	2	0	35	20	21	13	160	170	10	2		
5	160/75 (103)	165/70 (102)	4	1	39	28	25	17	142	146	12	4		
6	125/65 (85)	128/65 (86)	0	0	25	15	15	10	115	125	5	0		
7	150/80 (103)	150/80 (103)	2	0	30	26	20	18	140	150	5	0		
8	180/82 (115)	200/80 (120)	3	0	30	20	21	15	185	200	12	5		
9	115/75 (88)	110/75 (87)	0	0	33	22	21	14	115	110	10	2		
10	110/80 (90)	125/82 (97)	3	0	22	15	14	10	—	—	5	0		
Mean	(97.1)	(98.5)	1.8	0.1	29.6	19.7	18.8	13.1	133	140.7	8.2	1.9		
±SD	12.9	12.8	1.7	0.3	5.9	4.9	3.7	3.0	26.2	29.3	3.3	2.4		
±SE	4.1	4.1	0.5	0.1	1.9	1.6	1.2	1.0	8.7	9.8	1.1	0.7		
P value	NS		<0.02		<0.01		<0.01		NS		<0.001			

S_aO_2 = arterial oxygen saturation; P_aCO_2 = partial pressure of CO_2 in arterial blood; P_aO_2 = partial pressure of O_2 in arterial blood; V_E = minute ventilation (BTPS); P = significance of change between values obtained during control period and during phentolamine infusion.

most likely explanation; however, in our study the fall in the pulmonary artery pressure without a decline in the pulmonary vascular resistance does not conclusively support this contention.

Phentolamine is known to be an alpha-adrenergic blocking agent. This is based on the observation that it can antagonize or even reverse the pressor response to epinephrine (Meier *et al.*, 1949; Walker *et al.*, 1950); the blockade thus produced is relatively transient. A mild sympatholytic action becomes manifest only with the use of very large amounts of this agent (Freis, MacKay, and Oliver, 1951). The drug also has an obvious peripheral vasodilating effect which is not blocked by atropine (Goodman and Gilman, 1955). The drug's relatively weak sympathetic blocking action as well as its antagonism to the circu-

latory catecholamines cannot adequately explain the striking vasodilatation that results from its use under normal resting conditions.

Other hypotheses can be offered to explain the decline in the pulmonary artery pressure. Phentolamine by reducing airway obstruction could reduce endobronchial pressure and secondarily reduce pulmonary vascular pressures. None of our subjects had clinically evident bronchospasm, but it is not possible to exclude a direct mechanical effect on the pulmonary blood vessels mediated by bronchomotor activity. However, the comparable one-second forced expiratory volume obtained before and after phentolamine administration suggests that little change occurred in the airway obstruction. It has been shown that a reduction in hydrogen ion concentration is associated with pulmonary

arteriolar dilatation in patients with chronic lung disease (Enson *et al.*, 1964). In this study there was no correlation between the changes in arterial pH or $P_a\text{CO}_2$ and the reduction in pulmonary artery pressure. Phentolamine could reduce pulmonary artery pressure by increasing alveolar oxygen tension. It was shown in this study that phentolamine administration had a minimal effect on the $P_a\text{O}_2$ and the oxygen saturation.

Taylor *et al.* (1965a) cautioned against the use of the drug in reducing pulmonary hypertension, since in the dose they employed the decline in the systemic vascular resistance could be hazardous. However by using the low infusion rate of 0.3 mg/min this complication can be avoided.

This study suggests that the infusion of phentolamine at 0.3 mg/min may also be of benefit to patients with cor pulmonale. Further investigation of phentolamine's action in this condition is warranted.

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