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The use of a vasodilator, felodipine, as an adjuvant to long-term oxygen treatment in COLD patients

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The use of a vasodilator, felodipine, as an adjuvant to long-term oxygen treatment in COLD patients. T. Bratel, G. Hedenstierna, O. Nyquist, E. Ripe.
ABSTRACT: Eight patients with chronic obstructive lung disease (COLD) and pulmonary hypertension were given an infusion of a calcium antagonist, felodipine, during ongoing, long-term oxygen treatment (LTOT). The effects on central haemodynamics and ventilation-perfusion matching were studied. At rest pulmonary and systemic vascular resistances (PVR and SVR) were reduced by 18% (NS) and 26% ($p<0.05$), respectively. Cardiac output increased by 23%. There was a tendency to increased perfusion of low alveolar ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) areas ($\dot{V}_A/\dot{Q}<0.1$) and to increased shunt compared to pretreatment values. Arterial oxygen tension (Pao_2) fell by 0.7 kPa ($p<0.001$) but total oxygen transport increased by 23% ($p<0.001$). After treatment with oral felodipine (7.5–15 mg·day^{-1}) for a mean time of 14 wks, PVR and SVR were reduced by 16% ($p<0.05$) and 7% (NS), respectively, as compared to pretreatment values at rest. Cardiac output rose by 13%. The $\dot{V}_A/\dot{Q}$ ratios and the Pao_2 returned towards pretreatment values. The total oxygen transport increased by 11% ($p<0.05$) at rest and increased by 19% ($p<0.05$) during exercise as compared to the pretreatment value. The positive effect on central haemodynamics indicates that felodipine may be a valuable adjunct to ongoing LTOT.
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Patients with advanced chronic obstructive lung disease (COLD), and hypoxaemia often develop pulmonary hypertension. The prognosis for these patients is poor with a yearly mortality rate of around 30% [1]. In randomized controlled studies, domiciliary long-term oxygen treatment (LTOT) has proved to be one way of improving the survival rate of COLD patients with respiratory insufficiency [1–3]. Acute oxygen administration induced only minor changes in pulmonary haemodynamics, but after six months of oxygen therapy for 18 h per day clear reductions in mean pulmonary arterial pressure (Ppam) and pulmonary vascular resistance (PVR) were noted both at rest and during exercise [3]. However, those patients most severely afflicted by their disease did not respond to LTOT [1–3]. In another study a steep increase of the mortality rate was noted after 8 yrs of LTOT [4]. This calls for alternative methods of reducing the mortality rate in patients with COLD and respiratory insufficiency. In previous studies we have described a reduction in PVR in patients with severe COLD during peroral treatment with a calcium antagonist, felodipine [5]. We then hypothesized that administration of a vasodilator would also reduce PVR in patients with ongoing LTOT. This study reports on the effects of administering felodipine to COLD patients treated with LTOT.

Patients and methods

Eight patients who were all smokers or ex-smokers and who had suffered from severe COLD for at least 10 yrs were studied. They had all been on LTOT for at least 4 months (mean 33 months, range 4–96 months). The oxygen was given by nasal prongs at a mean flow rate of 1.6 $l \cdot min^{-1}$ in order to raise the arterial oxygen tension (Pao_2) to 8.0 kPa or more, and the patients used their oxygen for about 16 h per day or more. In addition to oxygen they were all on diuretics and oral and inhaled bronchodilators. Seven of the patients had undergone repeated phlebotomies because of secondary polycythaemia, and six had had episodes of acute right heart failure. One patient had an inherited deficiency of $alpha_1$-proteinase inhibitor. Another patient had undergone a rightsided thoracotomy because of pulmonary tuberculosis 40 yrs before the trial. Her total lung capacity was slightly reduced, but spirometry showed that her pulmonary disease was mainly obstructive (patient 8 in table 1). No patient was above 70 yrs of age. They had a mean forced expiratory volume in one second (FEV_1) of 23% of predicted normal and a mean Pao_2 of 6.6 kPa (in room air). For detailed patient data, see table 1.

Table 1. – Baseline patient data

No.	Sex	Age yrs	Body surface area m^2	FEV_1 % pred	TLC % pred	Max work capacity W	Pa_{O_2} (RA) kPa	Pa_{CO_2} (RA) kPa
1	F	46	1.65	23	117	55	6.9	6.4
2	M	55	2.10	21	146	65	6.7	6.4
3	M	69	1.59	25	-	-	6.4	7.0
4	M	68	1.95	18	119	56	6.3	6.8
5	M	70	2.04	21	95	74	7.2	7.5
6	F	46	2.87	18	123	45	6.5	7.6
7	F	61	1.73	27	113	40	5.9	7.6
8	F	64	1.90	32	59	67	6.7	8.1
Mean		60	1.85	23	110	57.4	6.6	7.2
±SEM		±3	±0.07	±2	±10	±4.6	±0.1	±0.2

FEV_1: forced expiratory volume in one second; TLC: total lung capacity; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; SEM: standard error of mean.

Catheterization

A triple-lumen catheter, Swan Ganz No. 7F (Edward's Lab), was positioned with its tip in the pulmonary artery, and short catheters were introduced into a peripheral vein and the brachial artery. Pressures were measured by capacitive transducers (Siemens Elema), using the mid-thoracic level as reference. Cardiac output was assessed by thermodilution in triplicate (Cardiac Output Computer, model 9520, Edward's Lab). For further details see [6].

Alveolar ventilation-perfusion relationship ($\dot{V}_A/\dot{Q}$)

The ventilation-perfusion match was assessed by a multiple inert gas elimination technique which made the analysis of a virtually continuous distribution of the $\dot{V}_A/\dot{Q}$ ratios possible [7]. For this purpose, six gases with different solubilities in blood dissolved in saline were infused into a vein at a rate of 3 $ml \cdot min^{-1}$ throughout the study. Samples of arterial and mixed venous blood were drawn and mixed expired gas was collected in matched glass syringes for subsequent analysis of the inert gas concentrations by the use of a gas chromatograph (Perkin-Elmer Sigma III) [8]. By measuring the retention and excretion of each gas and by making a formal mathematical analysis, a representative $\dot{V}_A/\dot{Q}$ distribution was obtained [9].

Other blood analyses

Arterial and mixed venous blood were drawn for blood gas analysis (equipment: ABL 2, Radiometer, Copenhagen). Arterial blood was also collected to assess the concentration of felodipine. For technical details see [10].

Study protocol

All patients were in a stable clinical condition with no sign of acute cardiac failure or respiratory tract infection at the time of the catheterizations. The day before their catheterization the patients underwent a complete spirometry and, if they were not too disabled, they performed a seated maximal bicycle ergometer test (in 6 out of 7 cases whilst receiving oxygen). The ordinary oxygen treatment was then continued without interruption in all patients until the catheterization protocol was terminated the next day. The ordinary medication was given regularly throughout the study. After catheterization a resting period of 15–20 min was allowed. Exercise in the supine position with an ergometer bicycle at an average work-load 1/4 of maximum (about 15 W) was then performed, and measurements of central haemodynamics and blood gases were executed. During a resting period of about 40 min, inert gases were infused (for assessment of $\dot{V}_A/\dot{Q}$) and central haemodynamics and gas exchange were measured at rest. An infusion of felodipine at a rate of 0.9 $mg \cdot h^{-1}$ was given and measurements of central haemodynamics and gas exchange were again performed at rest after 35 min of infusion. During continued felodipine infusion the patient performed a supine submaximal exercise at the same work-load as previously, and the same measurements were repeated. This protocol enabled as reliable as possible an analysis of felodipine effects at rest, since no exercise had been performed between recordings at rest before and during felodipine infusion.

The patients then continued with an oral felodipine dose of 7.5–15 $mg \cdot day^{-1}$ and were followed in the out-patient clinic every 2–6 wks by measurements of arterial blood gases and pulmonary X-ray. They were questioned about side-effects. The patients' ordinary medication and oxygen doses were maintained. After a mean treatment period of 14 wks (range 9–21 wks) a new spirometry was recorded and a bicycle exercise test during oxygen administration was performed. The low flow oxygen dose was continuously administered overnight until central haemodynamics and blood gases had been measured at rest and during exercise at the same work-load as during the earlier catheterizations.

Table 2. – Central haemodynamics of patients at rest, before felodipine treatment (C), after 35 min of felodipine infusion (FI), and during oral felodipine treatment (OF)

No.		QT $l \cdot min^{-1}$	HR beats·min^{-1}	SV ml	Ppam mmHg	Ppcw mmHg	RAP mmHg	BAP mmHg	PVR mmHg·l^{-1}·min	SVR mmHg·l^{-1}·min
1	C	5.5	93	59	26	6	7	95	3.6	16.0
	FI	6.6	109	60	26	7	7	94	2.9	13.2
	OF	6.4	102	63	30	8	10	105	3.4	14.8
2	C	7.0	107	66	28	9	7	98	2.7	13.0
	FI	8.9	107	83	31	9	5	95	2.5	10.1
	OF	6.2	104	60	25	8	7	90	2.7	13.4
3	C	3.8	89	43	30	11	6	-	5.0	-
	FI	-	-	-	26	11	6	-	-	-
	OF	5.0	96	52	31	11	4	96	4.0	18.4
4	C	4.6	82	56	29	10	7	106	4.1	21.5
	FI	5.2	78	67	31	10	10	80	4.0	13.5
	OF	5.1	-	-	28	10	6	105	3.5	19.4
5	C	5.1	89	57	30	13	12	87	3.3	14.7
	FI	5.8	87	67	22	13	8	79	1.6	12.2
	OF	6.3	76	83	30	13	9	89	2.7	12.7
6	C	5.6	107	52	42	11	7	96	5.5	15.9
	FI	6.1	110	56	44	11	9	86	5.4	12.6
	OF	7.1	105	68	39	13	12	89	3.7	10.8
7	C	4.2	103	41	18	7	6	90	2.6	20.0
	FI	5.7	112	51	22	8	5	75	2.5	12.3
	OF	5.3	111	48	23	9	5	94	2.6	16.8
8	C	5.4	85	64	27	10	12	92	3.2	14.8
	FI	6.3	82	77	29	10	12	89	3.0	12.2
	OF	5.5	77	71	24	7	4	95	3.1	16.6
Mean	C	5.2	94	55	28.8	9.6	8.0	94.9	3.8	16.6
	FI	6.4*	101	66*	28.9	9.9	7.8	85.4*	3.1	12.3*
	OF	5.9*	96	64	28.8	9.9	7.1	95.4	3.2*	15.4
SEM	C	±0.3	±4	±3	±2.3	±0.8	±0.9	±2.3	±0.4	±1.2
	FI	±0.5	±6	±4	±2.5	±0.7	±0.9	±2.9	±0.5	±0.4
	OF	±0.3	±5	±5	±1.8	±0.8	±1.0	±2.3	±0.2	±1.0

QT: cardiac output; HR: heart rate; SV: stroke volume; Ppam: mean pulmonary arterial pressure; Ppcw: primary capillary wedge pressure; RAP: right atrial mean pressure; BAP: brachial arterial mean pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance. Significantly different from pretreatment value; *: $p<0.05$.

Statistics

All data are presented as the mean±SEM. A two-sided paired t-test was used to assess the significance of a difference between values obtained before and during felodipine treatment. Values of $p<0.05$ were considered significant. Linear regression analysis was used to test the correlation between variables in response to acute or long-term felodipine treatment.

Results

Baseline data and effects of the felodipine infusion

Central haemodynamics. During control measurements at rest the pulmonary arterial mean pressure (Ppam) and pulmonary vascular resistance (PVR) were elevated, 29 mmHg and 3.8 mmHg·l^{-1}·min, respectively. With the patients resting in supine position, heart rate was increased and stroke volume was decreased, as compared to normals of the same age [11]. Right atrial pressure was at the upper limit of normal [12]. During supine, submaximal exercise before felodipine treatment, both the cardiac output and Ppam increased by about 60%, and PVR remained unchanged (tables 2 and 3).

After 35 min of felodipine infusion an increase in cardiac output of about 23% compared to resting values before felodipine ($p<0.05$) was noted. This increase was due to a significant increase ($p<0.05$) in stroke volume. The pulmonary arterial pressure did not change whilst the systemic arterial pressure fell by 9.5 mmHg ($p<0.05$). PVR fell by 18% although the reduction was not statistically significant. The systemic vascular resistance (SVR) was diminished by 26% ($p<0.05$). During exercise stroke volume increased by 14% ($p<0.05$) and cardiac output by 12% (NS) compared to exercise before felodipine. Pulmonary arterial pressures and PVR did not change significantly. The systemic arterial pressure and SVR were both significantly reduced, by 14 and 27%, respectively, (tables 2 and 3).

Table 3. – Central haemodynamics of patients during exercise, before felodipine treatment (C), during felodipine infusion (FI), and during oral felodipine treatment (OF)

No.		QT $l \cdot min^{-1}$	HR beats·min^{-1}	SV ml	Ppam mmHg	Ppcw mmHg	RAP mmHg	BAP mmHg	PVR mmHg·l^{-1}·min	SVR mmHg·l^{-1}·min
1	C	6.0	103	58	40	16	8	146	4.0	23.0
	FI	7.7	117	66	36	12	10	104	3.1	12.2
	OF	8.0	101	79	45	18	9	144	3.4	16.9
2	C	12.1	114	106	43	15	9	133	2.3	10.3
	FI	12.7	112	113	43	14	11	110	2.3	7.8
	OF	9.8	103	91	46	17	9	107	3.0	10.0
3	C	-	-	-	-	-	-	-	-	-
	FI	-	-	-	-	-	-	-	-	-
	OF	-	-	-	-	-	-	-	-	-
4	C	8.1	158	51	50	19	15	134	3.8	14.7
	FI	7.0	131	53	53	19	15	113	4.9	14.0
	OF	9.1	-	-	47	18	9	133	3.2	13.6
5	C	7.5	112	67	43	21	13	96	2.9	11.1
	FI	9.8	118	83	53	21	13	89	3.3	7.8
	OF	10.9	107	102	42	21	12	101	1.9	8.2
6	C	8.7	126	69	73	20	13	104	6.1	10.5
	FI	8.1	119	68	55	20	13	88	4.3	9.3
	OF	9.9	126	79	52	20	18	109	3.2	9.2
7	C	6.3	115	55	30	11	5	101	3.0	15.2
	FI	8.6	119	72	27	10	5	89	2.0	9.8
	OF	-	-	-	-	-	-	-	-	-
8	C	9.8	106	93	42	22	17	118	2.0	10.3
	FI	11.8	106	111	49	22	15	118	2.3	8.7
	OF	9.6	102	94	38	20	10	118	1.9	11.3
Mean	C	8.4	119	71	45.9	17.6	11.4	118.9	3.5	13.6
	FI	9.4	115	81*	45.1	16.7	11.7	102.7*	3.2	9.9*
	OF	9.6	109*	89	45.0	19.0	11.2	118.7	2.8	11.5
SEM	C	±0.8	±7	±8	±5.0	±1.5	±1.6	±7.3	±0.5	±1.8
	FI	±0.8	±3	±9	±3.9	±1.8	±1.3	±5.3	±0.4	±0.9
	OF	±0.4	±5	±5	±1.9	±0.6	±1.4	±6.8	±0.3	±1.3

For abbreviations, see table 2.

Table 4. – Blood gases and minute ventilation

	Before felodipine		During felodipine infusion		During oral felodipine	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
$\dot{V}_E$ $l \cdot min^{-1}$	9.0 ±0.8				9.1 ±0.7	
Pao_2 kPa	9.3 ±0.9	8.1 ±1.0	8.6*** ±0.8	7.8 ±0.8	9.3 ±0.9	8.1 ±0.6
$Paco_2$ kPa	7.2 ±0.4	7.5 ±0.5	7.1 ±0.4	6.8* ±0.5	7.6 ±0.4	7.0 ±0.3
$totO_2trp$ ml·min^{-1}	897 ±72	1227 ±97	1099*** ±83	1424 ±100	996* ±51	1459* ±57
$C(a\text{-}\bar{v})o_2$ ml·l^{-1}	55.9 ±2.2	79.4 ±5.9	45.9*** ±1.8	66.6 ±4.6	49.9* ±2.5	63.7 ±4.7

$\dot{V}_E$: minute ventilation; Pao_2: arterial oxygen tension; $Paco_2$: arterial carbon dioxide tension; $totO_2trp$: total oxygen transport = total oxygen content × cardiac output; $C(a\text{-}\bar{v})o_2$: arterial mixed-venous oxygen content difference. Significantly different from pretreatment value; *:

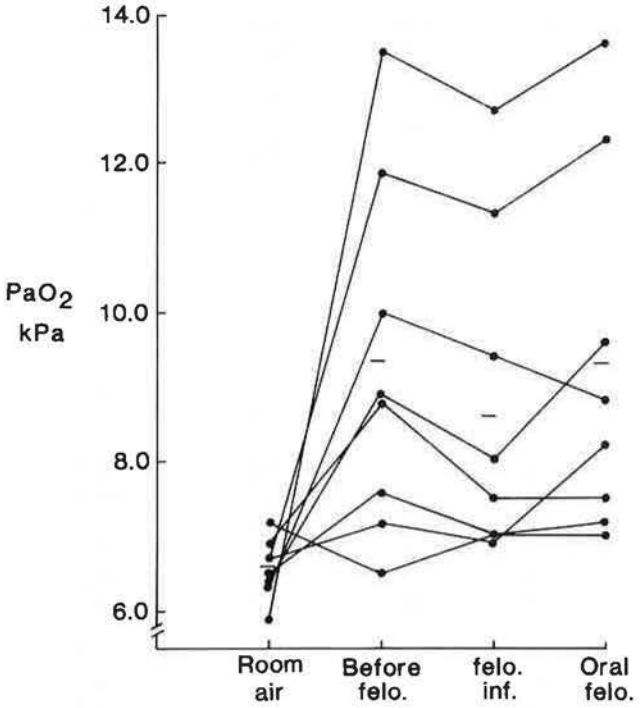

Fig. 1. – Individual arterial oxygen tensions at room air before felodipine treatment and during low flow oxygen treatment; before felodipine, during the felodipine infusion, and during oral treatment. mean values denoted by –.

Gas exchange. Pao_2 during oxygen treatment was on average 2.7 kPa higher than previously measured during air breathing ($p<0.05$) (measurements were made after 4 h or more of air breathing, 1–10 months earlier). There was no significant difference between arterial carbon dioxide tension ($Paco_2$) with or without oxygen treatment (tables 1 and 4 and fig. 1).

The Pao_2 was reduced by 0.7 kPa ($p<0.001$) at rest and by 0.3 kPa ($p<0.05$) during exercise compared to pretreatment data. However, due to the large increment in cardiac output, total oxygen transport increased by more than 20% at rest ($p<0.001$) and by 16% (NS) during exercise (table 4).

Ventilation-perfusion data were obtained in six patients and were measured only at rest (table 5). All patients had a considerable ventilation-perfusion mismatch with increased dispersion (log SD) of ventilation as well as of perfusion distributions (1.45±0.17 and 0.92±0.07, respectively). Shunt was negligible. There was a substantial amount of ventilation of high $\dot{V}A/\dot{Q}$ areas (regions with a $\dot{V}A/\dot{Q}$ ratio above 10). The felodipine infusion did not increase the scatter of ventilation or perfusion, but perfusion of low $\dot{V}A/\dot{Q}$ areas ($\dot{V}A/\dot{Q}$ <0.1) increased from a mean of 2 to 6%, and a small increase in shunt was noted (from 1 to 2%) (fig. 2 and table 5).

Dose-response relationship. There was a significant correlation between the increase in felodipine concentration and the reduction of PVR after 35 min of felodipine infusion ($r=0.83$, $p<0.05$). During exercise, however, there was no obvious dose-response relationship. No clear correlation between changes in SVR and felodipine concentrations could be found either at rest or during exercise.

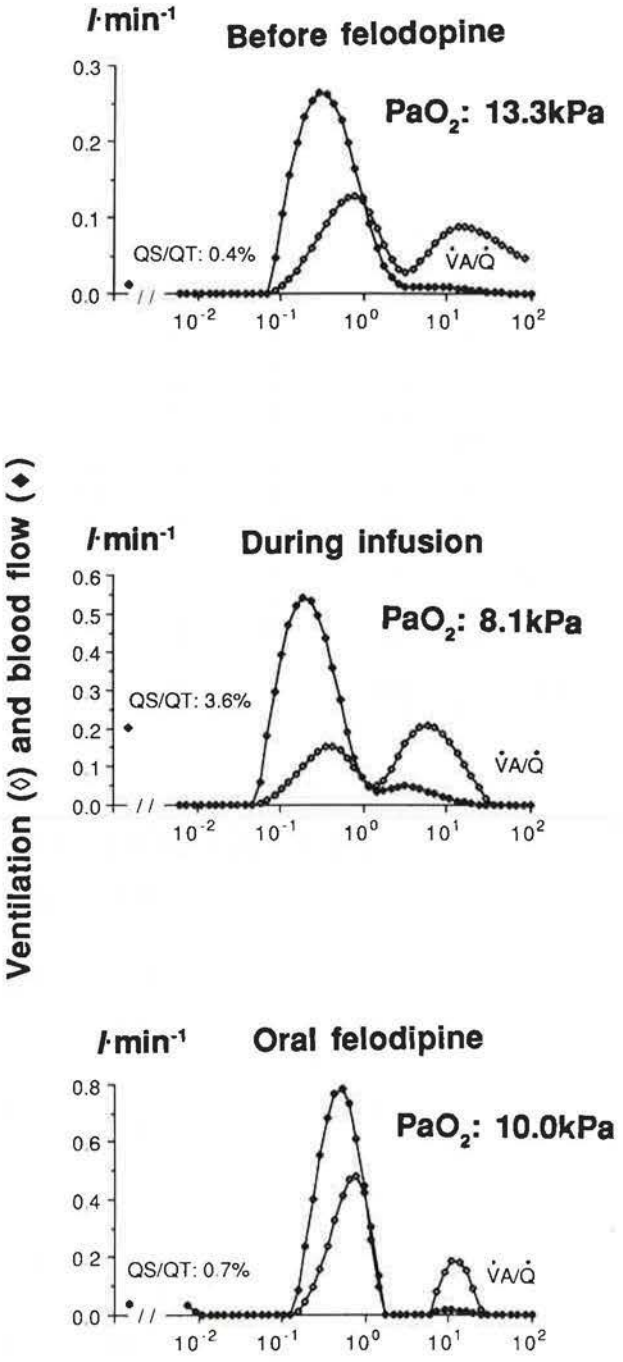

Fig. 2. – $\dot{V}A/\dot{Q}$ distributions (ventilation: open symbols; perfusion: closed symbols) at rest before felodipine, during felodipine infusion, and during oral felodipine treatment in patients no. 4. Note the increased shunt and perfusion of low $\dot{V}A/\dot{Q}$ areas ($\dot{V}A/\dot{Q}$: 0 and <0.1, respectively) during the felodipine infusion and the improvement of the ventilation-perfusion matching during oral treatment. $\dot{V}A/\dot{Q}$: ventilation-perfusion ratio.

Table 5. – Ventilation-perfusion data: mean $\dot{V}_A/\dot{Q}$ of ventilation ($\dot{V}_{mean}$) and perfusion ($\dot{Q}_{mean}$) and their log standard deviations ($\dot{V}_{SD}$, $\dot{Q}_{SD}$) and the fractional distributions of ventilation and perfusion to regions with different $\dot{V}_A/\dot{Q}$ ratios, (mean values±SEM)

	Before felodipine n=6	During felodipine infusion n=5	During oral felodipine n=4
$\dot{V}_{mean}$	2.34±0.45	1.48±0.23	1.30±0.23
$\dot{V}_{SD}$	1.45±0.17	1.42±0.17	1.17±0.17
$\dot{Q}_{mean}$	0.58±0.10	0.40±0.05	0.42±0.06
$\dot{Q}_{SD}$	0.92±0.07	0.93±0.10	0.81±0.10
Fractional distribution of $\dot{V}$ to $\dot{V}_A/\dot{Q}$:			
<1.0	0.25±0.04	0.27±0.05	0.29±0.03
<10	0.27±0.06	0.22±0.06	0.24±0.08
<100	0.09±0.03	0.05±0.03	0.03±0.02
>100	0.46±0.04	0.46±0.03	0.45±0.04
Fractional distribution of $\dot{Q}$ to $\dot{V}_A/\dot{Q}$:			
0	0.01±0.01	0.02±0.01	0.01±0.01
<0.1	0.02±0.01	0.06±0.02	0.02±0.02
<1.0	0.76±0.08	0.80±0.03	0.87±0.03
<100	0.22±0.08	0.12±0.02	0.11±0.02

Long-term treatment

Central haemodynamics. After an average treatment period of 14 wks with oral felodipine a significant increase in cardiac output ($p<0.05$) of 13% was noted as compared to pretreatment values. Heart rate remained unchanged and the increase in cardiac output was achieved entirely by an increase in stroke volume ($p=0.05$). Pulmonary and systemic arterial pressures remained unchanged. PVR was reduced by 16% ($p<0.05$) while SVR was reduced by only 7% (NS).

During exercise cardiac output was increased by 14% compared to the pretreatment value, and PVR decreased by 20%. However, because of the wide scatter of the changes, no significance was attained for either of these variables. Heart rate decreased significantly and SVR remained unaltered (for further details, see table 3).

Gas exchange. The ventilation-perfusion match reverted to a similar pattern as before felodipine treatment. The shunt decreased in two patients and the perfusion of low $\dot{V}_A/\dot{Q}$ areas ($\dot{V}_A/\dot{Q}$ <0.1) was reduced in three (table 5 and fig. 2). Blood gases remained essentially unchanged as compared to pretreatment values, but total oxygen transport increased by about 11% at rest ($p<0.05$) and by 19% during exercise ($p<0.05$) (table 4). Oxygen flux increased by 15% or more in four of the patients at rest and during exercise.

Dose-response relationship. After 14 wks of oral felodipine medication the mean plasma felodipine level was 8.1 nmol·l^{-1} (range 5.3–13.9 nmol·l^{-1}) at rest. Significant correlations between on the one hand reductions in PVR and SVR and on the other increasing felodipine concentration were found both at rest and during exercise (PVR, rest and exercise: $r=0.82$ and $r=0.83$, ($p<0.05$ for both), respectively; SVR, rest and exercise: $r=0.84$ ($p<0.05$) and $r=0.65$ (NS), respectively). At rest six of the eight patients responded with a reduction in PVR, whilst two remained unchanged (range of ΔPVR: 0–33%). There was a correlation between augment baseline Ppam and PVR on the one hand, and the reduction in PVR at rest during oral felodipine on the other ($r=0.90$ and $r=0.96$, $p<0.05$ and $p<0.06$, respectively). Patients with low Pao_2 during ongoing LTOT had a weak tendency to respond with a larger reduction in PVR at rest (Pao_2 *vs* ΔPVR: $r=0.57$; NS).

Clinical observations. All patients completed their trial period. Side-effects consisted of oedema of the lower extremities (six patients), transient tachycardia, headache and flushing (two patients). Because of the oedema a dose reduction was necessary in four patients. Four patients experienced an improvement of their subjective walking capability whilst one experienced a reduction. Working capacity measured by ergometer bicycle test tended to increase from 57±5 W (E.P.=131±5) to 61±7 W (E.P.=130±3) and there was a weak correlation ($r=0.60$; NS) between changes in working capacity and changes in PVR at rest before and during oral felodipine treatment.

Discussion

The major finding was that long-term oral felodipine treatment as an adjuvant to low flow, long-term oxygen treatment resulted in a sustained reduction in PVR in patients with advanced COLD and pulmonary hypertension. Indeed, the effect was more marked in the pulmonary than in the systemic circulation. In earlier studies on patients with less severe COLD, without LTOT, lowering of systemic vascular resistance has been more prominent and has even necessitated a lowering of the peroral dose or discontinuation of the treatment.

Comparison with previous studies

The patients in the present study, thus, had a more advanced pulmonary obstructive disease than those studied in a previous felodipine trial (FEV_1 23% of predicted *vs* 27%) and their pulmonary hypertension was more marked (Ppam 29 mmHg *vs* 23 mmHg [5]). The question thus arises whether the more selective and consistent reduction of PVR in the present study was due to the different degrees of lung disease or to the combination with oxygen treatment. In our earlier studies [5, 6], as well as in a study on the effect of nifedipine [13], the response to the calcium antagonist treatment was the same irrespective of the severity of airway obstruction and degree of pulmonary hypertension. On the other hand, in the present study a

correlation between initial Ppam and PVR and reduction of PVR by oral felodipine was noted. It is thus possible that the response to felodipine increases with increasing vascular resistance due to COLD, but that a severe vascular affliction is required to make the correlation obvious. Whether this is correct or not, the observation remains that the addition of the calcium antagonist to patients with COLD so advanced that they receive LTOT reduces their PVR at least during a mean 14 wk period of peroral felodipine.

Pulmonary hypertension

In a previous study no significant change in central haemodynamics was noted even during a three year observation period of patients with stable COLD [14]. All of our patients were in a stable condition and seemed well adjusted to their oxygen treatment. An important reason for selecting patients who had been on LTOT for an appreciable time for the study is that earlier investigations on long-term oxygen treatment in COLD patients such as the Medical Research Council (MRC) study [1] and the Nocturnal Oxygen Therapy Trial (NOTT) study [3] did not show any definite central haemodynamic and clinical effects until 17 and 6 months had passed, respectively. We have selected patients who had been on LTOT for an average period of 33 months. It is, therefore, reasonable to assume that optimal central haemodynamic effects of the oxygen treatment had been achieved and that the patients were in steady state with their LTOT. Acute administration of low dose oxygen to COLD patients slightly but significantly reduced stroke volume and cardiac output [3]. Measurements during room air breathing have shown that the reduction in PVR induced by 6–31 months LTOT is not accompanied by any significant change in cardiac output [3, 15]. After three months of felodipine treatment in addition to LTOT, a significant increase in cardiac output was noted in the present study. Stroke volume tended to decrease after 31 months of LTOT [15] whilst it tended to increase after 3 months of felodipine. We therefore conclude that the reduction in PVR observed during the additional long-term felodipine treatment was entirely due to felodipine and not to the concurrent LTOT.

The slow haemodynamic improvement by LTOT may be explained by experimental findings of release during hypoxia of a factor which is mitogenic for pulmonary smooth muscle cells [16]. This may be an important cause of the pulmonary vascular hypertrophy, noted in postmortem studies on COLD patients [17]. The vascular hypertrophy probably contributes to the pulmonary hypertension of these patients and an increased right ventricular afterload [18]. These morphological changes may require a long time before being reverted and it is thus not surprising that even one month of low flow oxygen treatment failed to induce significant improvement in pulmonary haemodynamics in patients with COLD [19]. It is also interesting to note that animal studies have shown that calcium antagonists attenuate the pulmonary vascular hypertrophy caused by hypoxia [20]. Thus, the combination of LTOT and a calcium antagonist may act synergistically to reduce the hypoxia-induced anatomical changes of the lung vasculature.

Gas exchange

The shunt in the patients that we studied was low or even absent, the mean being 1%. This is similar to earlier studies on patients, with advanced obstructive lung disease [21]. Since it is reasonable to assume regional complete airway occlusion in such patients the small shunt suggests efficient hypoxic pulmonary vasoconstriction. Collateral ventilation has been proposed as an additional mechanism to reduce shunt [22]. Felodipine infusion increased the shunt and the perfusion of low $\dot{V}_A/\dot{Q}$ regions, and this brought about a reduction in arterial oxygen tension of about 9%. This is again in accordance with previous observations [6, 23]. The deterioration of the ventilation-perfusion mismatch can reasonably be explained by a reduction of the hypoxic pulmonary vasoconstriction. In spite of the reduced Pao_2 both this and previous studies have shown an increased total oxygen transport due to the simultaneous increase in cardiac output [6].

It might be anticipated that oxygen breathing, even at low concentrations, creates unstable lung units with critically low $\dot{V}_A/\dot{Q}$ ratios, *i.e.* lung units with no or minimal expired ventilation. This will lead to alveolar collapse and development of shunt according to the theories put forward by DANTZKER *et al.* [24]. However, our patients did not have a larger shunt during LTOT than patients with advanced COLD studied earlier during air breathing [21]. This is also in line with previous findings of minimal increases in shunt in COLD patients during short periods of breathing pure oxygen [21]. Whether this reflects the absence of critically low $\dot{V}_A/\dot{Q}$ units or indicates that such units for some reason are protected from collapsing, *e.g.* because of fibrotic lesions, cannot be determined from the present study.

An interesting observation in the present study was that during long-term felodipine treatment the ventilation-perfusion pattern returned towards the one seen before acute felodipine treatment. Concurrently Pao_2 increased. The improvement in the ventilation-perfusion match can hardly be attributed to the attenuated effect of felodipine since PVR remained reduced and cardiac output remained increased as they were during the acute infusion of the drug. The mechanism is not clear, but a possibility is redistribution of ventilation towards lung units that receive an increased perfusion by the felodipine treatment.

Individual responses

The arterial oxygen tension during LTOT was significantly higher than in room air. The oxygen doses had been titrated during earlier hospital stays to raise Pao_2 above a value of 8.0 kPa, which was a therapeutic

goal of the MRC and NOTT oxygen trials [1, 2]. However, in two patients Pao_2 remained below 8.0 kPa on both catheterization occasions. There was a weak and nonsignificant tendency towards a larger reduction in PVR after long-term felodipine treatment among patients with low Pao_2 during concomitant LTOT. One might, therefore, argue that the hypoxic vasoconstriction was not optimally counteracted in all patients. There was, however, a wide scattering of the responses and two patients with a Pao_2 above 8.0 kPa responded with a reduction in PVR of 15% or more. Felodipine thus seems to have sustained pulmonary vasodilating effect at least in a subgroup of COLD patients with optimal oxygen therapy. Also, we decided not to change the oxygen dose during the trial period since a sudden change might have obscured the felodipine-induced haemodynamic effects.

Side-effects

The side-effects were similar to the ones seen in earlier studies on calcium antagonist treatment of COLD patients [5, 13]. Oedema of the lower extremities was due to felodipine-induced dilatation of resistance vessels and was not a sign of cardiac failure [25].

Conclusion

Felodipine treatment results in a sustained reduction of pulmonary vascular resistance and an increase in total oxygen transport in patients with COLD and ongoing LTOT, which suggests that this calcium antagonist may be of use as an adjuvant to the treatment of such patients. However, our results are preliminary and further studies are warranted.

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L'utilisation d'un vasodilatateur, la felodipine, comme adjuvant à l'oxygénothérapie au long cours chez les patients BPCO. T. Bratel, G. Hedenstierna, O. Nyquist, E. Ripe.

RÉSUMÉ: Huit patients, atteints de bronchopneumopathie chronique obstructive et d'hypertension pulmonaire, ont été traités par perfusions d'un antagoniste du calcium, la felodipine, au cours d'un traitement par l'oxygène (LTOT). Nous avons étudié les effets sur l'hémodynamique centrale et la congruence de la ventilation et de la perfusion. L'on a noté une diminution de 18% dans la résistance pulmonaire au repos (PVR) et de 26% dans la résistance vasculaire pulmonaire (SVR). La première différence était non significative, la seconde significative pour $p<0.05$. Le débit cardiaque a augmenté de 23%. L'on a noté une tendance à l'augmentation de la perfusion des zones à bas rapport ventilation alvéolaire-perfusion ($\dot{V}_A/\dot{Q}_A$) ($\dot{V}_A/\dot{Q}_A$ <0.01) et à une augmentation du shunt, par comparaison avec les valeurs avant traitement. La pression partielle d'oxygène artériel (Pao_2) baisse de 0.7 kPa ($p<0.001$), mais le transport total d'oxygène augmente de 23% ($p<0.001$). Après traitement par felodipine orale (7.5 à 15 mg par jour) pendant une durée moyenne de 14 semaines, PVR et SVR diminuent de 16% ($p<0.05$) et de 7% (NS), respectivement, par comparaison avec les valeurs au repos avant traitement. Le débit cardiaque augmente de 13%. Les rapports $\dot{V}/\dot{Q}$ et la Pao_2 retournent à des valeurs proches de celles précédant le traitement. Le transport total d'oxygène augmente de 11% ($p<0.05$) au repos, et augmente de 19% ($p<0.05$) au cours de l'effort, par comparaison avec les valeurs avant traitement. L'effet positif sur l'hémodynamique centrale indique que la felodipine pourrait être un appoint de valeur à l'oxygénothérapie au long cours déjà instaurée.

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