

## Cardiac function and central haemodynamics in severe chronic obstructive lung disease. Acute and long-term effects of felodipine

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*Cardiac function and central haemodynamics in severe chronic obstructive lung disease. Acute and long-term effects of felodipine. T. Bratel, G. Hedenstierna, H. Lundquist, O. Nyquist, E. Ripe.*

**ABSTRACT:** Eleven patients, with advanced chronic obstructive lung disease (COLD), received an infusion of the calcium antagonist felodipine at a rate of 0.9 mg/h. Pulmonary and systemic vascular resistances (PVR and SVR) at rest were reduced by 18% ( $p < 0.05$ ) and 33% ( $p < 0.001$ ), respectively. Cardiac output increased by 33%. The right ventricular and left ventricular ejection fractions (RVEF and LVEF), measured by equilibrium gated radionuclide ventriculography, increased by 32% ( $p < 0.01$ ) and 25% ( $p < 0.01$ ), respectively. During exercise both PVR and SVR fell by a mean of 30% ( $p < 0.01$ ). RVEF and LVEF both increased by about 14% ( $p < 0.05$  and  $p < 0.01$ ). After three months of oral felodipine treatment, a dose-related decrease in PVR was noted at rest ( $r = -0.83$ ) compared with pretreatment values. There was an increase in RVEF which correlated to a reduction in PVR ( $r = -0.76$ ). Three patients discontinued the trial due to side effects. It is concluded that the reduction of PVR induced by felodipine is accompanied by an improvement in right heart function as measured by ejection fraction measurements.

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In a previous study, we found that oral administration of the calcium antagonist felodipine for three months or more resulted in a reduction of PVR in five of nine patients with severe chronic obstructive lung disease (COLD) [1]. In the patients who responded with a PVR reduction, the stroke volume and the cardiac output were increased, but the pulmonary vascular pressures were essentially unchanged. The increase in stroke volume might have been a passive effect of an increased right ventricular end-diastolic volume or due to more efficient right ventricular emptying. The rate of this emptying is primarily determined by the right ventricular afterload [2]. To find out if felodipine treatment is accompanied by an improved right ventricular performance, a combined radionuclide and central haemodynamic study was carried out. Both the acute and long-term effects of felodipine treatment were investigated in patients with severe COLD.

### Patients and methods

Eleven patients with a history of severe COLD for at least five years participated in the study. Ten of the patients were smokers or exsmokers. Four patients had a history of right ventricular failure. No patient was above 70 yr of age at the time of the study. The eleven patients had a mean forced expiratory volume in one second ( $FEV_1$ ) of 27% of the predicted value and a mean arterial oxygen tension ( $PaO_2$ ) of 8.3 kPa

(table 1). All patients were receiving therapeutic doses of theophylline preparations and of oral and inhaled  $\beta_2$  agonists. Seven were being treated with oral and/or inhaled steroids and four with diuretics. The patients were in a stable clinical condition at the time of the study.

### Catheterization

A triple-lumen catheter, Swan Ganz No. 7F (Edward's Lab.), was positioned with its tip in the pulmonary artery, and a short catheter was introduced into a peripheral vein and the brachial artery. Pressures were measured by capacitive transducers (Siemens Elema, Stockholm) using the mid-thoracic level as reference. Cardiac output was assessed by thermodilution (Cardiac Output Computer, model 9250, Edward's Lab.). For further details, see [3].

### Radioventriculography (RVG)

The patients received 10 mg of stannous pyrophosphate intravenously. Their blood was then labelled and equilibrated with 740 MBq of  $^{99m}Tc$ -pertechnetate. Images of the heart were acquired in left anterior oblique (LAO) projection, with a General Electric gamma camera interfaced to a PDP 11/34 computer. The patients lay in supine position and the 30° slant hole collimator was individually adjusted to obtain maximum separation between the right and left ventricle of the heart. The gamma camera and the

Table 1. - Patient baseline data

Patient	Sex	Age yrs	Cardiac output at rest l/min	Body surface area m <sup>2</sup>	Total lung capacity % pred	FEV <sub>1</sub> % pred	Total haemoglobin % pred	PaO <sub>2</sub> kPa	PaCO <sub>2</sub> kPa	Max. working capacity W
1	F	59	3.7	1.64	110	23	78	10.5	5.5	58
2	F	55	4.8	1.40	152	19	149	6.5	6.6	46
3	M	63	5.3	1.88	128	-	-	9.2	4.5	80
4	F	65	4.3	1.67	100	23	116	6.3	7.4	64
5	F	45	6.2	1.58	128	21	139	7.1	8.1	70
6	F	64	4.3	1.58	141	36	114	8.8	5.7	73
7	M	58	5.8	1.88	114	20	104	7.8	6.2	56
8	M	70	4.6	1.56	88	38	101	8.4	5.0	40
9	F	55	4.6	1.52	141	37	131	8.5	5.8	80
10	M	60	4.2	1.69	142	31	108	8.6	5.4	58
11	M	65	5.0	1.85	112	24	85	10.0	4.4	70
$\bar{x}$		59.8	4.8	1.66	123.3	27.2	112.5	8.30	5.9	63.0
SD		6.8	0.7	0.16	20.1	7.5	22.5	1.30	1.1	13.0
SEM		2.1	0.2	0.37	6.0	2.4	7.1	0.40	0.3	3.9

patient were then 'fixed' in the same position, while the different images were collected by a standard, gated RVG-technique. The ventricles were outlined with a light pen, the large vessels and atria being excluded. The background was designated around the lateral border of the left ventricle (excluding the great vessels). From the images, the ejection fraction (EF) of the two ventricles was calculated using the equation,

$$EF = \frac{EDC - ESC}{EDC}$$

where EDC and ESC are the counts of radioactivity, within the background-corrected region of interest, at the end of diastole and systole for each ventricle. The EF was calculated by the same operator.

#### Study protocol

The patients gave their informed consent to the study, which was approved by the local Ethics Committee. The day before the catheterization the patients underwent exercise electrocardiogram (ECG), complete spirometry, pulmonary X-ray, and a physical examination. The patients were allowed to continue their regular medication without interruption throughout the study.

After introduction of the catheters the patients performed supine submaximal exercise (mean load of 11 W, approximately 1/3 of maximum).

Measurements of central haemodynamics and blood gases were made during exercise and the ejection fractions were measured immediately after completion of the exercise. The patient then rested for about 40 min to regain baseline resting condition and measurements of central haemodynamics, blood gases and ejection fractions were again performed. A continuous (*i.v.*) infusion of felodipine, at a rate of 0.9 mg/h, was then given and central haemodynamics, blood gases and ejection fractions were measured at rest after 35 min of infusion. During continued felodipine infusion, the patient then performed supine submaximal exercise at the same work load as before the infusion and the same measurements were repeated.

The patients were then given oral felodipine (5–10 mg twice daily) for about 3 months (11–15 weeks). Seven patients were able to complete the treatment period (see 'side effects'). At the end of the treatment period, the patients underwent a new exercise ECG and complete spirometry. Cardiac catheterization was performed and central haemodynamics, blood gases, felodipine concentrations and ejection fractions were measured, at rest and during exercise (same work load as three months earlier), about 2½–3 h after the intake of a tablet of felodipine (*i.e.* at the expected peak concentration [4]).

#### Statistics

A two-sided paired *t*-test was used to assess the significance of a difference between variables measured before and during drug treatment. All data are presented as mean ± SEM.

The change in RVEF and in other variables, in response to acute and long-term felodipine treatment, were compared by linear regression analyses.

## Results

#### *Cardiac function and central haemodynamics before and during felodipine infusion*

Resting pretreatment values showed an increased PVR in all patients, with a mean of 3.9 mmHg·l<sup>-1</sup>·min. The stroke volume was slightly subnormal (59 ml) [5] (table II). RVEF was lower than normal (in our laboratory), 28 versus 45% [6] (table 2). The left ventricular ejection fraction (LVEF) was slightly subnormal, 49 vs 55% [6]. The end diastolic volume of the two ventricles (RVEDV and LVEDV) was estimated by dividing the stroke volume by the ejection fraction of the right and left ventricle, respectively. RVEDV was approximately double LVEDV. During exercise before felodipine treatment, the cardiac output increased by about 50% and the mean pulmonary arterial pressure (Ppa) by 60%, resulting in an unchanged PVR. LVEF and RVEF rose by 25 and 14% respectively. The end-diastolic volumes did not change significantly (table 2).

After 35 min of infusion of felodipine, cardiac output was increased by 33% compared with the resting value before the infusion. This increase was associated with a significant increase in both the heart rate and stroke volume (table 2). The systemic arterial pressure had decreased by 12 mmHg. PVR was reduced by 18% (*p* < 0.05) and SVR by 33% (*p* < 0.001). Both RVEF and LVEF were significantly increased (by 32 and 25% respectively). The end-diastolic volumes did not change significantly (table II). During exercise, cardiac output rose by another 20%, compared with the exercise situation before the infusion. The mean Ppa fell by 5 mmHg. The PVR and SVR were both reduced by about 30%. The ejection fractions of the right and left ventricles both increased by about 13–14% (individual EF changes are depicted in fig. 1). RVEDV and LVEDV remained unchanged (table 2).

During the felodipine infusion Pao<sub>2</sub> at rest was reduced by 0.4 kPa (*p* < 0.01). The total oxygen transport (cardiac output × arterial oxygen content) rose by 35% at rest and 25% during exercise compared with pretreatment values (table 2).

#### *Cardiac function and central haemodynamics during long-term treatment*

Seven patients continued the felodipine medication throughout the trial period. The findings after treatment were compared with the pretreatment data in this group of patients (table 3). In six of the seven patients a second heart catheterization could be performed. At rest the felodipine treatment resulted in a significant increase in cardiac output of 36% (*p* < 0.01). PVR and SVR were reduced by about 20 and 25% respectively, but because of a wide scatter of

Table 2. - Central haemodynamics, radionuclide measurements and blood gases at rest and during exercise (mean values±SEM).

		Before felodipine		During felodipine infusion	
		Rest	Exercise	Rest	Exercise
		n=11		n=11	
QT	l/min	4.8±0.2	7.2±0.4	6.4±0.4***	8.8±0.5**
HR	beats/min	84±5	107±5	95±5*	115±6
SV	ml	59±4	68±3	68±3***	77±4
P <sub>pa</sub>	mean	25±3	41±3	26±2	36±2*
	wedge	7±1	13±1	7±1	13±1
RAP	mean	5±1	9±1	4±1	8±1
BAP	mean	96±4	124±5	84±3**	109±3**
PVR		3.9±0.4	4.1±0.6	3.2±0.4*	2.9±0.4**
SVR		19.4±1.1	16.9±1.5	12.9±0.8***	12.0±0.9**
		n=11		n=10	
RVEF	%	28±3	35±3	37±4**	40±5*
LVEF	%	49±3	56±2	61±2**	63±2**
RVEDV	ml	268±62	203±22	207±34	229±42
LVEDV	ml	124±12	120±9	110±5	120±8
		n=11		n=11	
PaO <sub>2</sub>	kPa	8.3±0.4	7.3±0.4	7.9±0.3*	7.1±0.5
PaCO <sub>2</sub>	kPa	5.8±0.4	6.3±0.4	5.7±0.3	6.2±0.4
TOT.O <sub>2</sub> TRP	ml/min	881±47	1276±99	1189±94**	1599±124**
C(a-V)O <sub>2</sub>	ml/l	48.5±1.7	75±4	39.8±1.8**	68.7±2

QT: cardiac output; HR: heart rate; SV: stroke volume; P<sub>pa</sub>: pulmonary arterial pressure; RAP: right atrial pressure; BAP: brachial arterial pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; RVEF and LVEF: right and left ventricular ejection fractions; RVEDV and LVEDV: right and left ventricular end diastolic volumes; TOT.O<sub>2</sub>TRP: total oxygen transport=total oxygen content x cardiac output; C(a-V)O<sub>2</sub>: arterial-mixed venous oxygen content difference. Significant differences from pretreatment values: \*p<0.05; \*\*p<0.01; \*\*\*p<0.001. Pressures in mmHg; resistances in mmHg.l<sup>-1</sup>.min<sup>-1</sup>

the changes these reductions did not attain significance. The pulmonary vascular pressures remained essentially unaltered.

During exercise PVR was reduced by 14% (NS) and SVR by 27% (p<0.05), (for further details, see table 3).

At rest RVEF increased from 30%, before felodipine administration, to 34% after 3 months of treatment, NS and during exercise, from 37 to 44% (p=0.09). No significant changes in LVEF or the end-diastolic volumes were noted (table 3). Total oxygen transport at rest was increased by 35% (p<0.01) (table 3).

#### Dose-response relationships

The plasma concentrations of felodipine in arterial samples were assayed in a previously described manner [3, 7]. After 35 min of felodipine infusion, at a rate of 0.9 mg/h, the mean plasma felodipine concentration was 22.9±1.0 nmol/l. There was a clear

inverse correlation at rest between felodipine concentration and the reduction in SVR, but not between the fall in PVR and increasing felodipine concentrations.

When the patients were recatheterized after three months of oral felodipine treatment, the mean plasma felodipine level at rest was 7.4 nmol/l (range 1.7-17.9 nmol/l). Increasing felodipine concentrations correlated significantly with reductions in PVR (r=-0.83). During exercise three out of six patients responded with a reduction in PVR compared with the pretreatment value, but no dose-response relationship was seen.

#### Correlation of ejection fractions with other variables

During the felodipine infusion at rest there was a significant correlation between changes in RVEF (ΔRVEF) and changes in cardiac output (ΔQT) (r=0.66). ΔPVR correlated with Δ stroke volume (r=0.67) but not with changes in any other variable. During oral felodipine treatment at rest ΔPVR and

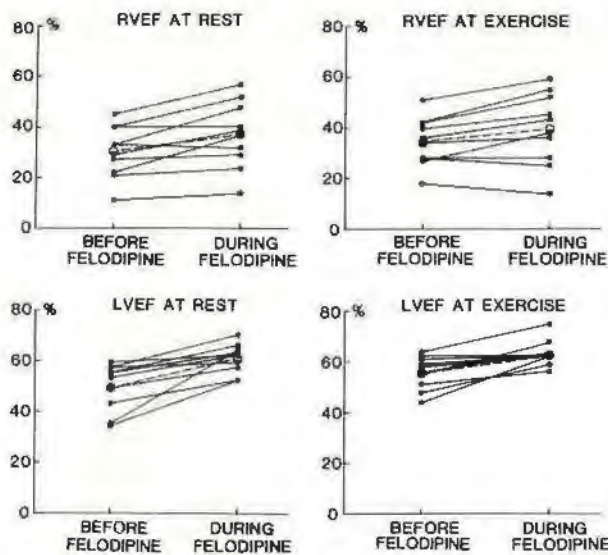


Fig. 1. Individual responses of right and left ventricular ejection fractions (RVEF and LVEF) to felodipine infusion at rest and during exercise. Broken line denotes average values. Note the more variable effect on the right ventricular ejection fraction.

$\Delta$ RVEF were inversely correlated in addition to  $\Delta$ SVR and  $\Delta$ LVEF ( $r = -0.76$  and  $r = -0.77$ , respectively) (see fig. 2).

During exercise, after three months of oral felodipine treatment, the only significant correlation that was noted was between  $\Delta$ PVR and  $\Delta$ RVEF ( $r = -0.70$ ).

#### Other observations

The physical working capacity, as measured by an ergometer bicycle test, was not changed after three months of oral felodipine therapy. There was no significant change in any spirometric variable.

Four patients spontaneously reported a reduction in obstructive symptoms. There was no consistent change in general feeling of well being and no clear correlation between changes in PVR and changes in subjectively or objectively measured physical capacity.

#### Side effects

Seven of the eleven patients noticed oedema of the lower extremities. Six patients experienced transient

Table 3. - Central haemodynamics, radionuclide measurements and blood gases at rest and during exercise (mean values  $\pm$  SEM) after three months of oral felodipine treatment.

		Before felodipine		During oral felodipine	
		Rest	Exercise	Rest	Exercise
		n=7	n=6	n=7	n=7
QT	l/min	5.0 $\pm$ 0.3	7.8 $\pm$ 0.6	6.8 $\pm$ 0.5**	9.9 $\pm$ 0.7
HR	beats/min	83 $\pm$ 7	108 $\pm$ 7	85 $\pm$ 8	113 $\pm$ 0.9
SV	ml	62 $\pm$ 5	73 $\pm$ 4	84 $\pm$ 11*	90 $\pm$ 9
P <sub>ra</sub>	mean	24 $\pm$ 4	40 $\pm$ 3	26 $\pm$ 3	44 $\pm$ 4
	wedge	6 $\pm$ 1	13 $\pm$ 1	7 $\pm$ 1	14 $\pm$ 1
RAP	mean	5 $\pm$ 1	9 $\pm$ 1	7 $\pm$ 0	11 $\pm$ 1*
BAP	mean	97 $\pm$ 6	117 $\pm$ 5	98 $\pm$ 8	116 $\pm$ 6
PVR		3.6 $\pm$ 0.4	3.5 $\pm$ 0.3	2.9 $\pm$ 0.4	3.0 $\pm$ 0.3
SVR		18.7 $\pm$ 1.3	14.6 $\pm$ 1.4	14.1 $\pm$ 2.4	10.7 $\pm$ 0.8*
		n=7	n=6	n=7	n=7
RVEF	%	30 $\pm$ 5	37 $\pm$ 5	34 $\pm$ 4	44 $\pm$ 6
LVEF	%	51 $\pm$ 3	57 $\pm$ 3	52 $\pm$ 2	60 $\pm$ 2
RVEDV	ml	298 $\pm$ 96	212 $\pm$ 36	283 $\pm$ 7	243 $\pm$ 66
LVEDV	ml	127 $\pm$ 16	126 $\pm$ 13	157 $\pm$ 18	146 $\pm$ 16
		n=7	n=7	n=7	n=7
PaO <sub>2</sub>	kPa	8.8 $\pm$ 0.5	7.7 $\pm$ 0.3	9.0 $\pm$ 0.7	7.4 $\pm$ 0.6
PaCO <sub>2</sub>	kPa	5.7 $\pm$ 0.5	6.1 $\pm$ 0.5	5.8 $\pm$ 0.5	6.3 $\pm$ 0.4
TOT.O <sub>2</sub> TRP	ml/min	921 $\pm$ 68	1425 $\pm$ 111	1239 $\pm$ 102**	1711 $\pm$ 107
C(a- $\bar{V}$ )O <sub>2</sub>	ml/l	48.2 $\pm$ 2.2	76.1 $\pm$ 5.5	47.6 $\pm$ 3.9	70.3 $\pm$ 9.7

Abbreviations, see table II

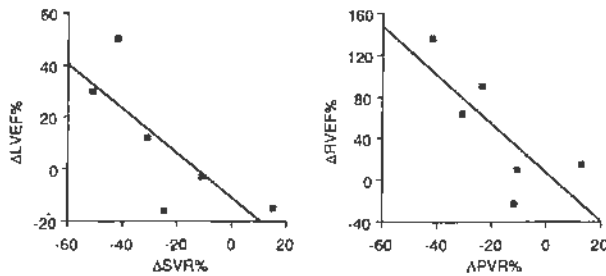


Fig. 2. The relationship between individual changes in systemic vascular resistance ( $\Delta$ SVR%) and in left ventricular ejection fraction ( $\Delta$ LVEF%) (left panel) as well as in pulmonary vascular resistance ( $\Delta$ PVR%) and the changes in right ventricular ejection fraction ( $\Delta$ RVEF%) (right panel), during oral felodipine treatment at rest, in comparison with pretreatment data ( $r = -0.77$  and  $r = -0.76$  respectively). For further details, see text.

headache. Four complained of dizziness and five of occasional or reiterated episodes of tachycardia.

In three patients the medication was discontinued due to side effects: in one because of episodes of supraventricular flutter; in one due to postural hypotension and dizziness; and in one because of a feeling of depression and general weakness (no reduction in systemic blood pressure was recorded).

Another patient contracted a long-lasting respiratory tract infection and was therefore excluded from the study.

In two of the seven patients who were able to complete the study, a dose reduction was necessitated by side effects.

## Discussion

### The method

Rather weak correlations have been found between RVEF and indices of disturbed pulmonary circulation, partly because of the difficulty in designating an accurate background correction when measuring ejection fractions with radionuclide ventriculography [2, 8, 9]. The inverse correlation between RVEF and mean pulmonary arterial pressure ( $r = -0.54$ ) in our study is comparable with the results of other investigators [2, 8, 9].

None of our patients had radiological signs of left ventricular failure or a history of coronary heart disease and they all had a normal exercise ECG. In spite of this and in accordance with other studies [6], five of the eleven patients had a subnormal LVEF ( $< 55\%$ ).

During exercise, image acquiring is difficult due to body movements. We therefore performed ejection fraction measurements during a period of about 5 min immediately following exercise. An exercise-induced increase in RVEF was noted before drug treatment in the present study, in contrast with other studies on COLD patients [10], where RVEF decreased when measured during exercise. However, RVEF was quantified in the same manner in connection with exercise before and during treatment. A comparison between these measurements should therefore be relevant.

### Haemodynamic effects

During the acute infusion of felodipine, there was no significant correlation between the changes in PVR and RVEF. However, there was a significant correlation between changes in RVEF and changes in cardiac output ( $r = 0.66$ ), possibly indicating that during short-term trials RVEF is to some extent sensitive to changes in flow [8] and therefore is also dependent on preload. Other investigators have presented varying degrees of correlation between changes in PVR and in RVEF during acute pharmacological trials in patients with COLD and pulmonary hypertension [9, 11]. During oral felodipine treatment, an inverse correlation was found at rest between changes in PVR and changes in RVEF ( $r = -0.76$ ) (fig. 2). When cardiac output increased during exercise before treatment, the increase was accompanied by a much higher increase in pulmonary driving pressure (mean pulmonary arterial pressure minus wedge pressure) than that which followed upon the felodipine-induced increase in cardiac output at rest (fig. 3). Although the number of patients is small, these data suggest that felodipine exerts its action to a large extent by active vasodilation of the pulmonary vasculature and that thereby an afterload reduction of the right ventricle is achieved.

After three months of oral felodipine medication, the vascular resistances seem to be the major determinants of the ejection fractions. During the felodipine infusion (*i.e.* the acute experiment) this relationship is possibly obscured by baroreflex reactions and other acute adjustments. To our knowledge, no previous study has addressed the long-term effects of vasodilator therapy on PVR and RVEF in the individual patients with pulmonary hypertension.

A calculation of RV stroke work ( $RVS\dot{W} = \text{stroke volume} \times 0.0136 \times (P_{\text{pam}} - \text{RAPm})$  (gm) (where  $P_{\text{pam}}$  is mean pulmonary arterial pressure and  $\text{RAPm}$  is mean right atrial pressure) shows that  $RVS\dot{W}$  is increased by oral felodipine from  $16.4 \pm 2.7$  to  $22.1 \pm 4.3$  gm at rest,  $p < 0.05$ , and from  $32.3 \pm 4.6$  to  $39.0 \pm 4.3$  gm during exercise (NS). However, this increase was entirely due to an increased stroke volume. In spite of this increment in stroke volume, the RV end-diastolic volume remained unchanged, implying that felodipine renders RV stroke work more efficient.

### Comparison with other studies

Of all the vasodilating agents which have been tried in acute studies in pulmonary hypertension secondary to COLD, the calcium antagonist nifedipine is one that has been most extensively studied. Acute administration of nifedipine may cause a reduction in PVR by about 30% [12–14]. At rest, during long-term treatment (2 weeks to 2 months), a sustained decrease of the PVR ( $-20\%$ ) and a significantly improved oxygen delivery have been reported [12, 13]. There were no signs of definite clinical improvement.

In the present study, oral felodipine treatment at rest, like nifedipine, resulted in a reduction of PVR of about 20%. This reduction in PVR in the individual

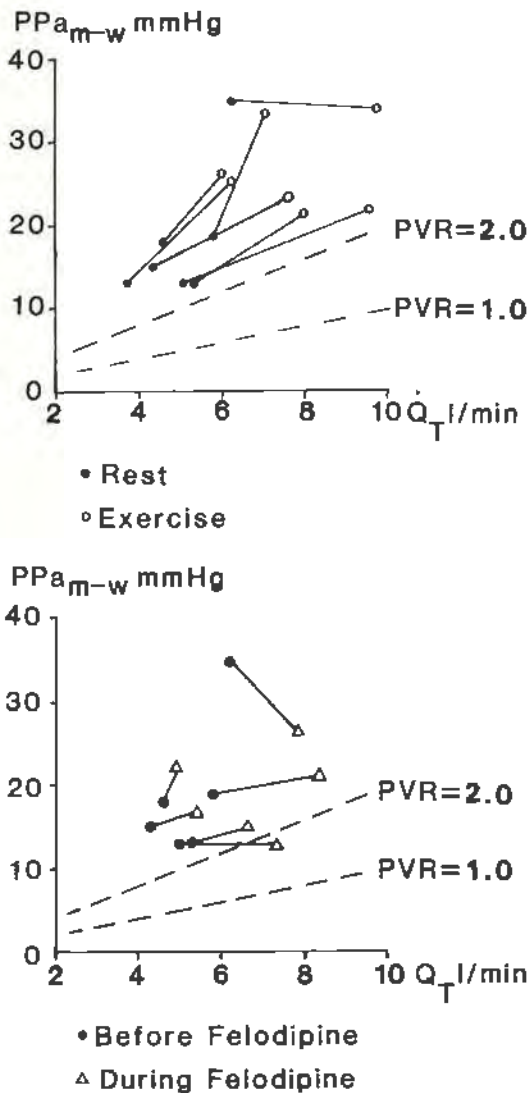


Fig. 3. *Upper panel:* The relationship between pulmonary driving pressure (mean arterial pulmonary minus wedge pressure,  $P_{pa-m-w}$ ) and cardiac output ( $Q_T$ , at rest (closed circles) and during exercise (open circles) before felodipine treatment. *Lower panel:* The relationship between  $P_{pa-m-w}$  and  $Q_T$  at rest before felodipine treatment (closed circles) and at rest during oral felodipine treatment (open triangles). Note the tendency towards a reduction of  $P_{pa-m-w}$  in relation to  $Q_T$  with felodipine treatment (i.e. a flatter slope of the pressure-volume curves than the PVR isopleths).

subject is accompanied by an improvement of right heart function as measured by right ventricular ejection fraction measurements. The improvement of right ventricular performance is probably explained by a reduction of right ventricular afterload. Due to frequent side effects careful supervision is needed.

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**RÉSUMÉ:** 11 patient atteints de forme avancée de BPCO ont reçu une perfusion de Félodipine (antagoniste calcique) au taux de 0.9 mg/h. Au repos, les résistances vasculaire, pulmonaire et systémique étaient réduites de 18% ( $p < 0.05$ ) et de 33% ( $p < 0.01$ ) respectivement. Le débit cardiaque a augmenté de 33%. Les fractions d'éjection ventriculaire droite et gauche, mesurées par ventriculographie isotopique à l'équilibre, ont augmenté respectivement de 32% ( $p < 0.01$ ) et de 25% ( $p < 0.01$ ). Pendant l'effort, la résistance vasculaire, pulmonaire et systémique a baissé en moyenne de 30% ( $p < 0.01$ ) tandis que les fractions d'éjection ventriculaire droite et gauche augmentaient d'environ 14% ( $p < 0.05$  et  $p < 0.01$ ). Après trois mois de traitement oral à la Félodipine, on a noté une diminution de la résistance vasculaire pulmonaire, en relation avec la dose, par comparaison avec les valeurs de pré-traitement, au repos ( $r = -0.83$ ). D'autre part, il y avait une augmentation de la fraction d'éjection ventriculaire droite en relation avec la réduction de la résistance vasculaire pulmonaire ( $r = -0.76$ ). Trois patients ont interrompu l'essai pour effets collatéraux. On conclut que la réduction de la résistance vasculaire pulmonaire induite par la Félodipine est accompagnée d'une amélioration de la fonction cardiaque droite qui se traduit par les mesures de fraction d'éjection.