A Comparison of Two Long-Acting Vasoselective Calcium Antagonists in Pulmonary Hypertension Secondary to COPD*

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Study objectives and patients: Pulmonary hypertension (PH) is common in COPD and may predict mortality in this disorder. We have compared the pulmonary vasodilator effects, dose-response characteristics, and tolerability of two calcium channel blockers, amlodipine and extended-release (ER) felodipine, in 10 patients (seven men, age 68±4.8 [SD] years) with clinically stable COPD and PH.

Design: Drugs were given in equal single daily oral doses (2.5, 5, and 10 mg), increasing weekly for 3 weeks, in a randomized investigator-blinded crossover manner with a 1-week wash-out period between the two treatments.

Measurements: Doppler measurements of pulmonary hemodynamics were made on the seventh day of treatment at each drug dose. Lung function, arterial blood gases, and adverse events were also monitored weekly.

Results: A dose-dependent decline of pulmonary artery pressure (PAP) was observed with each drug. A dose of 2.5 mg produced a significant decrease in PAP compared with baseline (20% amlodipine, 17% felodipine ER). Additional decreases in PAP were observed at 5 mg and 10 mg that were similar for both drugs, but did not reach statistical significance compared with 2.5 mg. There was a dose-related decrease in pulmonary vascular resistance and increase in oxygen delivery with amlodipine and felodipine ER. Lung function and blood gas values were stable throughout. Side effects (headache and ankle edema) were less frequent during amlodipine treatment (p<0.05).

Conclusions: Both amlodipine and felodipine ER, given as a single daily oral dose of ≥2.5 mg, are effective pulmonary vasodilators in COPD patients with PH. Their dose-response characteristics are similar, but amlodipine treatment was associated with fewer side effects.

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Key words: amlodipine; COPD; felodipine; pulmonary hypertension; vasodilatation

Abbreviations: ACCm=mean acceleration to peak velocity; AoP=systemic BP; BSA=body surface area; CaO2=arterial oxygen content; CI=cardiac index; CO=cardiac output; Dco=diffusing lung capacity; ER=extended-release formulation; ET=ejection time; HR=heart rate; LTOT=long-term oxygen treatment; LVO=left ventricular outflow; PAP=pulmonary artery pressure; PEP=preejection period; PH=pulmonary hypertension; PVR=pulmonary vascular resistance; RVO=right ventricular outflow; SaO2=oxyhemoglobin saturation of arterial blood; SVR=systemic vascular resistance; TPVR=total pulmonary vascular resistance

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Pulmonary hypertension (PH), a common complication of COPD, is one of the major predictors of mortality in this disease.1,2 Pulmonary arterial pressure (PAP) in COPD can be lowered acutely by pharmacologic means3-7 or by oxygen supplementation.8,9 Long-term oxygen treatment (LTOT) is used widely in the management of COPD and is usually prescribed in patients with severe hypoxemia or those with moderate hypoxemia and cor pulmonale.9,11 However, LTOT is relatively cumbersome...
and intrusive, and most patients do not use it for more than 12 to 15 h/d. Also, patients with the most severe COPD have the least reduction in PH with LTOT.9,11

The administration of vasodilator drugs has been proposed as an alternative or adjunct to oxygen supplementation in the treatment of PH in COPD for a number of years. However, there remains considerable controversy regarding the likely benefits of vasodilators.6,12,13 Reports of worsening ventilation/perfusion inequality,14,15 a lack of long-term effectiveness (or development of tolerance),3,16 or excessive incidence of side effects16 have raised doubts about the benefits of a vasodilator treatment in COPD.

Nifedipine is the most extensively studied vasodilator in both primary PH and PH secondary to COPD.3,4,17-20 However, novel dihydropyridines with higher vascular selectivity and more prolonged durations of action are potentially superior for long-term treatment of PH secondary to COPD.21-24 We recently showed that felodipine given twice daily markedly improved pulmonary hemodynamics in pulmonary hypertensive and hypoxemic COPD patients.24 Pulmonary vasodilatation in that study was sustained for 3 months of treatment, without the development of tolerance or any deterioration in gas exchange. However, the incidence of felodipine side effects was such that we considered it might significantly impede a large-scale, placebo-controlled clinical trial.

Amlodipine is a new calcium antagonist with very high vascular (arteriolar) selectivity, prolonged duration of action that allows once daily administration, and it has a lower incidence of side effects than nifedipine.25 Felodipine extended release (ER) is an ER preparation that has similar advantages. Both preparations have a relatively small peak to trough plasma concentration difference across a 24-h period, which may lead to a reduced incidence of side effects.26 These agents are therefore potentially suitable for prolonged treatment of PH secondary to COPD.

The purpose of the present study was therefore to (1) compare the pulmonary vasodilator effects, dose-response characteristics, and side effect profiles of amlodipine and felodipine ER in patients with clinically stable COPD and PH, and (2) establish the optimal effective dose of a dihydropyridine vasodilator in the treatment of PH secondary to COPD.

**MATERIALS AND METHODS**

The research protocol used in this study was approved by the Ethics Committees of the Repatriation General Hospital, Daw Park, and Flinders University Medical Centre, Bedford Park, in South Australia. All patients gave written informed consent.

**Patient Selection**

Patients were recruited from the outpatient departments of the above institutions. For entry they were required to have a diagnosis of chronic bronchitis and/or emphysema secondary to cigarette smoking, to have been in stable condition with no clinical exacerbation in the preceding 2 months and to have had stable hypoxemia (PaO2 <70 mm Hg) over the same period. Evidence of chronic airflow limitation (FEV1 <60% predicted and FEV1/FVC ratio <60%) was also required. Measurements of pulmonary hemodynamics were made using Doppler ultrasound and it was necessary therefore to show clearly visible Doppler flow envelopes of the left and right ventricular outflows in each patient. Pulmonary hypertension (Doppler-estimated systolic PAP > >30 mm Hg and mean PAP >20 mm Hg) was also required for inclusion in the study.

Patients were excluded if they had any of the following: (1) history of asthma or >20% increase in FEV1 following bronchodilator; (2) history of primary cardiac disease or documented ischemic heart disease; (3) use of β-blocking drugs, antiarrhythmic agents, nitrates, or other vasodilators through the study period; (4) hemoglobin <12 g/100 mL; and (5) any severe concomitant disease that could interfere with survival or well-being (eg, renal failure, unstable diabetes, cancer). Patients older than 75 years were also excluded. Concomitant medications and oxygen therapy were kept constant throughout the study period.

Withdrawal criteria were as follows: (1) unwillingness on the part of the patient to continue; (2) acute exacerbation of COPD (eg, infective bronchitis) during the study period; or (3) the development of any serious side effects significantly affecting quality of life (eg, persistent severe pedal edema or headache).

Fifteen patients met the lung function and clinical entry criteria and were selected for Doppler screening. Thirteen patients had an analyzable Doppler signal for hemodynamic calculations and 11 of them met the criteria for pulmonary hypertension (see above) and were included in the trial. One patient was withdrawn from the trial after the first week because of an acute infective exacerbation of COPD. The baseline characteristics of the 10 patients (seven male and three female) who entered all phases of the study protocol are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1—Baseline Characteristics of COPD Patients (n=10)</th>
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<tbody>
<tr>
<td><strong>Range</strong></td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Smoking history, pack-yr</td>
</tr>
<tr>
<td>FEV1, L BTPS</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
</tr>
<tr>
<td>FVC, L BTPS</td>
</tr>
<tr>
<td>FVC, % predicted</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
</tr>
<tr>
<td>Dco,a, % predicted</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>SaO2, %</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
</tr>
</tbody>
</table>

*aBTPS=body temperature pressure saturated; Dco=diffusing lung capacity.*
Study Design

Five of the 10 patients recruited for the study were receiving continuous supplemental oxygen at a flow rate of 2 L/min. Amlodipine and felodipine ER were administered as a single daily oral dose for 3 weeks each, using an open-blind (open for patients, blinded for investigators) crossover design with 1-week wash-out period between the two treatments. Patients were administered increasing doses (2.5, 5, and 10 mg) of felodipine ER or amlodipine at 1-week intervals. The order of drug administration was randomized and blinded for the investigators by the hospital pharmacist. Doppler echocardiographic measurements of pulmonary hemodynamics were made on the seventh day of treatment at each drug level (steady-state) breathing room air to assess the effectiveness of pulmonary vasodilatation. Lung function and arterial blood gas measurements were monitored weekly to confirm the stability of lung function over the study period.

Assessment of Treatment Compliance and Side Effects

Patients were encouraged to report any side effects immediately. At each visit, patients were questioned about any adverse events and their answers were recorded. Patients were asked to categorize the side effects as mild, moderate, or severe, subject to the interference with their lifestyle. Compliance with the treatment was assessed by counting residual tablets.

Assessment of Cardiopulmonary Function

At the predetermined study visits, measurements were made of forced expiratory lung volumes (Morgan Spirometer; Kent, England), resting arterial blood gases (ABL 3 Blood Gas Analyzer; Radiometer; Copenhagen, Denmark), and Doppler echocardiography (Acuson Computed Sonography System; Mountain View, Calif) to assess pulmonary hemodynamics.27-29 Lung carbon monoxide transfer factor (Morgan TT Auto Link System; Kent, England) was measured at the beginning of the trial only.

Pulsed Doppler echocardiography was performed using 2.5- and 3.5-MHz transducers and with the patient at rest in the 30° left lateral decubitus position with a 20° upper body tilt. The transducer was positioned in the midleft parasternal border for the right ventricular outflow signal and in the apical position for the left outflow and mitral signals. Standard two-dimensional views were used.

An ECG signal with 0.04-s marks was displayed with the Doppler signals for event timing purposes. Tracings were recorded on videotape and on a strip-chart recorder at a sweep speed of 100 mm/s. All measurements were made from the outer borders of the darkest portion of the Doppler flow profiles.

Systolic and mean PAP and cardiac output (CO) were estimated as described below.

Doppler Estimation of PAP: The technique described by Morera and al27 was used to obtain estimates of PAP. In brief, at least four beats, preferably consecutive, were analyzed from each interrogated site, and average values were calculated for the following parameters measured from the right and left ventricular outflow tracings: prejection period (PEP), ejection time (ET) and mean acceleration to peak velocity (ACCM). The empirically derived index “F” was used to compare pressure-related right- and left-sided flow velocity (waveform) characteristics, using the measurements of PEP, ET, and ACCM in terms of their proportionality to pressure: F=PEP×ACCM/ET. As ACCM can be calculated by dividing peak velocity by acceleration time, F was calculated from Doppler trace measurements as follows: F=PEP×peak velocity/ET×acceleration time.

The F index for the right ventricular outflow (FrV0) is proportional to pressure in the pulmonary artery and is described by the equation FrV0=k(PAP). Similarly the F index for the left ventricular outflow (FlV0) is proportional to aortic (systemic) BP (AoP) and is described by the equation FlV0=k(AoP). Therefore, FrV0/FlV0=PAP/AoP, which was rearranged for the calculation of the PAP: PAP=FrV0/FlV0×AoP.

BP of the right arm at rest was taken at the beginning and the end of each Doppler study with appropriately sized arm cuffs and standard calibrated sphygmomanometer. Average systolic and diastolic values of BP were used for calculations. Mean systemic BP was calculated as one-third systolic+two-thirds diastolic BP.

Doppler Estimation of Stroke Volume and CO: Stroke volume and CO were estimated by the “nongeometric” technique described by Spodick and Koito.28 The basis of this technique is the relationship: stroke volume=ejection time×ejection rate. The left ventricular ejection time can be precisely measured from Doppler aortic flow traces. The ejection rate can be determined indirectly from Spodick and Koito’s regression equation: mean left ventricular ejection rate (mL/s)=494×Doppler mean aortic flow velocity (mV [m/s])−66. CO was simply derived by multiplying stroke volume by heart rate (HR) recorded at the time of Doppler measurement: CO=(494×mV−66)×ET×HR.

Our own validation studies29 show that the Doppler methods described above provide reliable estimates of PAP and CO, with high reproducibility. Using our regression equations for Doppler vs catheter values of PAP, we defined PH as being present if the Doppler estimate of “true” mean PAP was ≥20 mm Hg and systolic PAP was ≥30 mm Hg.

Calculations and Derived Indices: Total pulmonary vascular resistance (TPVR) was calculated by dividing mean PAP by CO, and systemic vascular resistance (SVR) was calculated by dividing mean AoP by CO. Cardiac index (CI) was calculated by dividing CO by body surface area (BSA). BSA was calculated from the following formula: BSA (m²)=weight (kg)×0.425×height (cm)×0.725×0.007184. Hemoglobin level and oxyhemoglobin saturation (SaO₂) were obtained from the blood gas analyzer, and arterial oxygen content (CaO₂) was calculated from the following formula: CaO₂=(1.34×hemoglobin)×SaO₂+0.003×PaO₂. Oxygen delivery was derived by multiplying CaO₂ by CI.

Statistical Analysis

The data were first subjected to a repeated measures analysis of variance test. If the F statistic for a particular parameter reached statistical significance (p<0.05), then pairwise comparisons were performed using the Newman-Keuls procedure. The difference in frequency of side effects between the two treatments was compared using the χ² test.

RESULTS

Compliance and Side Effects

Compliance with treatment during the study period was high and averaged 100±0.4% (mean±SD). The frequency and the severity of the side effects during felodipine ER and amlodipine treatments are shown in Table 2. Amlodipine treatment was associated with significantly less frequent and less severe side effects (headache and ankle edema) than felodipine ER in our study population. Side effects during amlodipine treatment were all mild and

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Table 2—Side Effects

<table>
<thead>
<tr>
<th>Symptom Days, No. (%)</th>
<th>Amlodipine</th>
<th>Felodipine ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>9 (13)</td>
<td>13 (19)</td>
</tr>
<tr>
<td>5</td>
<td>1 (1.4)</td>
<td>35 (50)*</td>
</tr>
<tr>
<td>10</td>
<td>13 (19)</td>
<td>36 (60)*</td>
</tr>
<tr>
<td>Individual side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing (mild)</td>
<td>6 (2.2)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Headache (mild)</td>
<td>4 (1.9)</td>
<td>30 (15)*</td>
</tr>
<tr>
<td>Headache (moderate-severe)</td>
<td>0</td>
<td>14 (7)*</td>
</tr>
<tr>
<td>Ankle edema (mild-moderate)</td>
<td>16 (7.6)</td>
<td>48 (24)*</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>0</td>
<td>7 (3.5)*</td>
</tr>
</tbody>
</table>

*p<0.05 (χ² test) compared with amlodipine.

relatively infrequent: headache, ankle edema, and facial flushing were reported by two patients each. Side effects during felodipine treatment were more frequent and troublesome to patients and appeared to be dose dependent. The most common side effect during felodipine treatment was headache (seven patients), followed by ankle edema (five patients), facial flushing (two patients), and GI problems (two patients). One patient developed severe headache and moderate ankle edema while receiving 5 mg of felodipine ER and withdrew from the last dose step (10 mg). Another patient asked to be withdrawn after completing 4 days of receiving the last dose step of felodipine ER because of exacerbation of his ulcer disease with severe abdominal pain, which he believed was associated with the treatment. Hemodynamic and lung function measurements were made on day 4 of the last dose increment in this patient.

Respiratory Function

Lung function and arterial blood gas variables are presented in Table 3. There were no statistically significant differences in any of the variables over the study period. Lung function was stable throughout the study. Neither drug adversely affected arterial oxygen tension.

Hemodynamics

The hemodynamic effects of amlodipine and felodipine are shown in Table 4. Each patient showed a decline in mean PAP with both amlodipine and felodipine and the maximal effects on individual mean PAPs are shown in Figure 1. There was a dose-response relationship for both medications that is shown in Figure 2. A dose of 2.5 mg produced a statistically significant decrease of mean PAP compared with baseline (p<0.05) for amlodipine (20%) and felodipine ER (17%) treatments. There was no difference between the vasodilator effects of the two drugs. The decreases in PAP compared with baseline observed at 5 mg (amlodipine and felodipine ER both 26%) and 10 mg (amlodipine 29%; felodipine ER [n=9]) 35% were somewhat greater but were not statistically significant compared to 2.5-mg dose effects. An increase in CO (maximum 12% amlodipine; 14% felodipine ER; not significant) was statistically significant only for the 10-mg dose of amlodipine (Fig 3). TPVR decreased significantly during amlodipine, but not during felodipine ER treatment. Oxygen delivery increased during both treatments, but due to the high variance of the individual data, it reached statistical significance only for the 10-mg dose of amlodipine (14%) and 5-mg dose of felodipine ER (16%). There was also a small, but statistically significant decrease in mean systemic arterial pressure (10% amlodipine; 6% felodipine ER) at the 10-mg dose. Maximal decrease for SVR (19% amlodipine, 15% felodipine ER) was less than half of the corresponding decrease in TPVR. Improvements in hemodynamic parameters were sustained during the 3-week treatment periods with each drug and returned to baseline levels after the 1-week washout periods between treatments.

Table 3—Respiratory Function During the Study Period (n=10)*

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂, mm Hg</td>
<td>60±3.0</td>
<td>60±2.8</td>
<td>62±2.7</td>
<td>60±2.6</td>
<td>61±3.1</td>
<td>61±2.9</td>
<td>61±2.8</td>
<td>63±2.5</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>42±2.0</td>
<td>42±1.7</td>
<td>43±1.7</td>
<td>43±1.7</td>
<td>42±1.6</td>
<td>42±1.7</td>
<td>42±1.8</td>
<td>41±1.9</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>90±1.3</td>
<td>91±1.2</td>
<td>91±1.0</td>
<td>90±1.1</td>
<td>91±1.2</td>
<td>91±1.0</td>
<td>91±1.2</td>
<td>92±0.7</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>30±4.2</td>
<td>32±4.4</td>
<td>31±3.9</td>
<td>32±3.9</td>
<td>31±3.7</td>
<td>33±4.4</td>
<td>32±3.6</td>
<td>35±4.1</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>72±5.7</td>
<td>75±4.8</td>
<td>75±5.1</td>
<td>77±4.9</td>
<td>77±5.0</td>
<td>79±4.9</td>
<td>78±5.4</td>
<td>82±4.8</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>29±3.1</td>
<td>29±3.4</td>
<td>29±2.9</td>
<td>31±3.9</td>
<td>30±4.0</td>
<td>30±4.2</td>
<td>30±3.2</td>
<td>29±2.8</td>
</tr>
</tbody>
</table>

*Values shown are mean±SEM.

* n=9 (one patient withdrew from the last dose step during felodipine ER treatment). There were no statistically significant changes in any of the variables across the study period.
Table 4—Hemodynamics and Oxygen Delivery (n=10)*

<table>
<thead>
<tr>
<th></th>
<th>Amlodipine</th>
<th>Felodipine ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, mg</td>
<td>0</td>
<td>2.5</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>40.1±5.4</td>
<td>31.9±3.6</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>85.9±3.6</td>
<td>83.5±2.9</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>82.4±5.7</td>
<td>87.6±5.1</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>6.99±0.4</td>
<td>7.28±0.4</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>3.98±0.2</td>
<td>4.17±0.3</td>
</tr>
<tr>
<td>TPVR, dyne s cm⁻⁵</td>
<td>508±118</td>
<td>374±60i</td>
</tr>
<tr>
<td>O₂ delivery, mL/min/m²</td>
<td>72.7±4.1</td>
<td>77.0±5.4</td>
</tr>
<tr>
<td>Mean systemic BP, mm Hg</td>
<td>96.9±2.9</td>
<td>91.8±2.5i</td>
</tr>
<tr>
<td>SVR, dyne s cm⁻⁵</td>
<td>1,144±76</td>
<td>1,040±69i</td>
</tr>
</tbody>
</table>

*All the values shown are mean±SE.

†n=9 (one patient withdrew from the last dose step during felodipine ER treatment).

‡p<0.05 compared with baseline (0 mg). There were no statistically significant differences in any of the variables between equivalent doses of amlodipine and felodipine ER.

**DISCUSSION**

The main finding of this study is that a 2.5-mg single daily oral dose of either amlodipine or felodipine ER resulted in significant pulmonary vasodilation in COPD patients with no adverse effects on arterial oxygen tension. Moreover, oxygen delivery to the tissues significantly increased due to a rise in CO. Amlodipine treatment was associated with significantly fewer side effects than felodipine ER. Higher drug doses in our patients appeared to produce increased vasodilation, but during felodipine ER,
Figure 2. PAP dose-response during treatment with amlodipine and felodipine ER. Asterisk = p<0.05, compared with baseline.

this significantly increased the frequency and the severity of side effects (headache and ankle edema).

Vasodilatation

The results of this trial are similar to our previous study of felodipine,\textsuperscript{24} which showed marked improvements in pulmonary hemodynamics in pulmonary hypertensive, hypoxemic COPD patients that were sustained during 12 weeks of treatment. Maximal decreases in mean PAP (29\% amlodipine, 35\% felodipine ER) and TPVR (39\% amlodipine, 50\% felodipine ER) in the present study were greater than in our earlier study of felodipine (22\% decrease in mean PAP, 32\% decrease in TPVR). As in our previous study, oxygen delivery was increased due to a rise in CO. The beneficial pulmonary vasodilatory effects were accompanied by a small decrease in mean systemic arterial pressure, but this was not associated with postural hypotension.

Some investigators have been unable to demonstrate a decrease in PAP with calcium channel antagonists despite a decrease in pulmonary vascular resistance (PVR),\textsuperscript{21,30} while others have shown a clear reduction of PAP.\textsuperscript{23,24} A possible explanation for the variable response to vasodilators in COPD is the selection of patients. For example, two studies that reported no change in PAP\textsuperscript{21,30} selected patients on the basis of a diagnosis of COPD not on the presence of PH. In these studies, the patients had a mean PAP that was barely above the normal range, and it is therefore not surprising that pulmonary vasodilation was slight and PAP unchanged. In contrast, vasodilatation was clearly demonstrated in other studies that enrolled patients with definite PH.\textsuperscript{22,24}

Side Effects

The incidence of side effects of felodipine ER treatment in the present study was higher than with amlodipine, and was similar to that found in our previous study.\textsuperscript{27} To our knowledge, the treatment and side effect profiles of amlodipine and felodipine
ER have not been compared previously in pulmonary hypertensive COPD patients. Koenig,31 who compared 5 and 10 mg of amlodipine and felodipine ER in a younger population (n = 118, mean age of 56 years) of patients with borderline systemic hypertension, found both treatments to be equally effective. The incidence of side effects in that study was lower than in the present study and was identical in amlodipine and felodipine groups. In contrast, a double-blind, double-dummy, randomized comparative study of amlodipine and felodipine ER in mild to moderate essential hypertension32 showed significantly more headache and flushing in the felodipine ER group. Our findings are similar to those reported in the latter study. One possible reason for these observed differences in side effects is amlodipine’s superior plasma drug concentration-time profile to ER felodipine.33

Gas Exchange

Our data confirmed that both amlodipine and felodipine ER did not adversely affect gas pulmonary exchange over two 3-week treatment periods. Although some investigators have reported increased ventilation/perfusion inequality and a fall in PaO2 with short-term administration of nifedipine14,15 and felodipine,21,22,30 studies evaluating longer-term oral treatment with nifedipine,19,20 nitrendipine,23 and felodipine21,22,24 found no significant difference. Most of the studies have shown that even when PaO2 is reduced, an increase in oxygen delivery to the tissues occurs due to an increased CO.19-24

Methodologic Considerations

We assessed drug compliance using the standard method of tablet counting. This was conducted independently by the hospital pharmacist at the weekly study visits and the data indicate a very high compliance rate in our patients. We have no reason to doubt these compliance data, although additional confidence in the assessment of compliance may have been possible by measuring drug plasma concentrations. Unfortunately, such methods were not available to us at the time.

Figure 3. CO dose-response during treatment with amlodipine and felodipine ER. Asterisk = p<0.05, compared with baseline.
ACKNOWLEDGMENTS: We wish to acknowledge David Scheinberg and Vicky Fitzgerald (Respiratory Function Unit, Repatriation General Hospital, Daw Park) for their technical assistance.

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