Acute and Chronic Calcium Antagonist Treatment Elevates Sympathetic Activity in Primary Hypertension

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Abstract

Eleven men with mild to moderate primary hypertension were studied at rest and during mental stress before and during intravenous infusion of the calcium antagonist felodipine. Eight of them were restudied during long-term treatment (extended-release felodipine, 10 mg daily). For comparison, 10 normotensive control subjects were studied with the short-term protocol. Heart rate, cardiac output, central cardiovascular pressures, and forearm blood flow were registered. Arterial and venous sampling was performed. Norepinephrine spillovers to arterial plasma and from the forearm were assessed with the use of radiotracer methodology. In the hypertensive patients, felodipine lowered mean arterial blood pressure acutely by 8% (P<.01). Systemic vascular resistance decreased by 22% (P<.001), cardiac output increased by 20% (P<.01), and norepinephrine spillover to arterial plasma increased by 61% (P<.001). Forearm vascular resistance fell by 30% (P<.001), but norepinephrine overflow from the forearm increased by 115% (P<.001). These forearm responses were not seen in normotensive subjects despite similar systemic responses to felodipine infusion. After 8 weeks of treatment, mean arterial pressure decreased to 15% below baseline (P<.001), cardiac output returned toward pretreatment levels, and systemic vascular resistance remained low. Forearm blood flow returned toward basal levels, but forearm vascular resistance remained lowered. Total body and forearm norepinephrine spillover values were as elevated as in the acute situation. The hemodynamic "defense reaction" and the sympathoadrenal response to mental stress were essentially unaffected by felodipine. Stress-induced small elevations of neuropeptide Y-like immunoreactivity persisted during felodipine. Thus, the vasodilatation induced by felodipine elicits sympathetic counterregulation, which persists in the long term with respect to peripheral and total sympathetic activities, despite resetting of the baroreflex control of heart rate. (Hypertension. 1994;24:287-296.)

Key Words: calcium channel blockers • felodipine • epinephrine • norepinephrine • stress, psychological • neuropeptide Y • hypertension, primary

Felodipine is a dihydropyridine-type calcium antagonist with high selectivity for resistance vessels. Acute hemodynamic responses of hypertensive humans to felodipine include dose-dependent reductions of systemic vascular resistance (SVR) and forearm vascular resistance (FVR) and reflexogenic elevations of heart rate and cardiac output. Venous plasma concentrations of norepinephrine (NE) increase after short-term administration of the drug, suggesting sympathetic counterregulation to the blood pressure lowering. However, unchanged venous plasma NE has been reported during short-term treatment in patients already treated with diuretics and β-blockers. During long-term treatment with felodipine the tachycardia disappears, probably because of adaptation of the arterial baroreflex, suggesting that sympathetic nerve activity might return to normal levels. Nonetheless, elevated venous plasma NE levels have been reported also during long-term (2 to 8 weeks) treatment. Thus, there may be discrepancies between cardiac and peripheral sympathetic readjustments to chronic vasodilator treatment with a dihydropyridine calcium antagonist, if venous plasma NE reflects relevant sympathetic activity. Venous plasma NE concentrations are commonly used to assess sympathetic activity in humans, but it is not always appreciated that cubital sampling overemphasizes local NE release (sympathetic activity in the forearm) and may poorly reflect sympathetic activity in the rest of the circulation. Assessments of the latter require measurements of arterial NE levels and, for increased precision, measurements of NE clearance from and NE spillover to arterial plasma by isotope dilution methodology. Such information seems to be lacking for vasodilator treatment with calcium antagonists. Therefore, the question still remains to what extent there is sympathetic counterregulation when hypertension is treated with a calcium antagonist of the dihydropyridine type, such as felodipine. The possibility that chronically elevated sympathetic activity might influence adaptive phenomena in vascular smooth muscle and the heart underlines the importance of elucidating the extent and time course of sympathetic counterregulation to vasodilator treatment. Measurements of arterial NE concentrations and spillover rate yield good information on sympathetic activity in general but do not reveal variations of sympathetic activity to different organs. Since in previous work the most common site for blood sampling has been the arm, it is also of interest to specifically study NE turnover in the forearm. NE overflow from the forearm may be accurately assessed by use of an isotope dilution method.
Sympathetic nerve activity is comparatively low under resting, unstressed conditions. It is therefore of interest to include a stimulus for increased sympathetic activity when interactions between treatment for primary hyper-tension and the autonomic nervous system are being studied. We chose mental stress, which activates the sympathetic nervous system and is relevant for the everyday life of patients. In human experimental situations, mental stress induces a defense reaction–like hemodynamic response, with increases of heart rate, cardiac output, mean arterial pressure, and vascular resistance in the splanchnic organs and the kidneys and decreases of vascular resistance in skeletal muscle.\textsuperscript{13,16}

The main aim of the present study was to investigate the extent and time course of sympathoadrenal counterregulation to blood pressure reduction with the calcium antagonist felodipine. We therefore studied hemodynamic changes, plasma catecholamine concentrations (arterial and venous), and NE turnover in the systemic circulation in relation to hemodynamic variables during short-term and long-term (2 months) treatment. In addition, we examined NE turnover in the regional vascular bed (the forearm), which has been the site for blood sampling for catecholamine measurements in previous studies. The study also examined whether the acute sympathetic counterregulation to felodipine treatment differed in hypertensive patients and normoten-sive control subjects and whether sympathoadrenal and cardiovascular responses to mental stress were modified by such treatment.

\textbf{Methods}

The study was performed in accordance with institutional guidelines and was approved by the Ethics Committee of the Karolinska Hospital and the Isotope Committee of Danderyd Hospital. Informed consent was obtained from all individuals.

\textbf{Subjects}

Eleven male patients with mild to moderate primary hypertension with a known duration of 1 to 15 (mean, 5.4) years and resting supine diastolic blood pressures of 95 to 115 mm Hg were studied. Previous antihypertensive medication was withdrawn at least 1 month before the study and consisted of \textbeta\textsubscript{-}adrenergic receptor blockade in 4 patients, calcium antagonists of the dihydropyridine type in 2, angiotensin-converting enzyme inhibitors in 3, and a combination of \textbeta\textsubscript{-}adrenergic receptor antagonists and dihydropyridine calcium antagonists in 2. The patients were compared with an age-matched group of 10 male healthy volunteers with resting diastolic blood pressures less than 85 mm Hg. There were no significant differences in height, weight, or body surface area between the two groups. The groups will be referred to as hypertensive patients and control subjects or, when taken together, as subjects.

\textbf{Procedures and Assays}

The subjects arrived in the laboratory in the morning after a light breakfast. Smoking and caffeine-containing beverages were not allowed on the day of investigation. With the subject in the supine position, a 5-lumen Gould thermomix catheter (7.5 F model SP 5507 H) was inserted percutaneously into an antecubital vein using the Seldinger technique. The tip was positioned in the pulmonary artery under fluoroscopic guidance. An arterial catheter (1.05 × 300 mm, British Viggo) was inserted into the brachial artery of the same arm for measurements of intra-arterial pressure and blood sampling. A short intravenous cannula (Venflon, Viggo-Spectramed) was introduced into an antecubital vein of the other arm and advanced 3 cm in the proximal direction for blood sampling.

Pressures were measured using Siemens Elema transducers 746 and amplifier 863 with a low-pass filter with a cutoff frequency of 7.5 Hz. Pressures were registered on an electrostatic recorder (ES1000, Gould Instruments SAF) together with an electrocardiographic lead and the temperature tracing from the thermodilution computer. Midthoracic depth, measured at the level of the fourth parasternal intercostal space, was used as reference. This level was marked on the subject with him in the supine position, and the pressure transducers were subsequently adjusted to the heart level with the subject in the semirecumbent position. Systolic and diastolic pressures in the pulmonary artery and the mean pressure in the right atrium were measured. Systolic and diastolic brachial arterial pressures (SAP and DAP) were measured. Mean pressures of the brachial and pulmonary arteries were calculated as the diastolic pressure plus one third of the pulse pressure. Heart rate was calculated from the electrocardiographic tracing (averaged over 30-second periods).

Cardiac output was determined by the thermomix technique with 5 mL injections of ice-cold 5.0% glucose. Curve analyses were performed with a thermomix cardiac output computer (model 9510 A, Edwards Laboratories). Values were obtained as the means of triplicate or, initially during mental stress, duplicate measurements. Temperature tracings on the electrocardiographic recorder were checked for artifacts and baseline drift. Single measurements deviating more than 25% and showing baseline drift were discarded.

Forearm blood flow (FFB) was determined by a mercury-in-Silastic strain-gauge venous occlusion plethysmograph (FE Hokansson Inc) in the nondominant arm with simultaneous occlusion of the wrist above the arterial pressure in order to exclude the circulation to the hand. Flow curves were recorded on a pen recorder (Houston Instruments). Each value was based on the mean of four to six curves. The arm was elevated and supported so that the forearm was slightly above the heart level. SVR and FVR were calculated as the ratios between mean arterial pressure and cardiac output and FBF, respectively.

Mental stress was induced by a modified version of Stroop's color word conflict test (CWT).\textsuperscript{17} A videotape shows color words written in incongruent colors, and simultaneously a voice gives a third conflicting color word for each word shown. The words are shown rapidly, and the subject is asked to mark the color he sees on a protocol where the color words are randomly listed and to disregard the two conflicting pieces of information. Hemodynamic responses to this mental stress test have reached a steady state within 8 to 10 minutes and have been shown to be reproducible.\textsuperscript{18}

Tritiated norepinephrine (1\textsuperscript{L}-\textsuperscript{3}H\textsubscript{NE}, 13.8 Ci/mmol, New England Nuclear) was prepared for human use and stored at −80°C until used. It was diluted in ice-cold saline containing ascorbic acid immediately before use. Storage did not influence the composition of the stock solution of \textsuperscript{3}H\textsubscript{NE}, as checked by the analytical techniques described below. The \textsuperscript{3}H\textsubscript{NE} was infused in the right atrium via the Gould catheter at a rate of 0.35 μCi·m\textsuperscript{−1}·min\textsuperscript{−1}. For further details see Hjemdahl et al.\textsuperscript{19}

Blood samples were collected simultaneously from the brachial artery and the antecubital vein into ice-chilled test tubes containing EDTA (10 mmol/L, final concentration) for determinations of NE and epinephrine or aprotinin (500 000 kal-like units per liter final concentration) for determinations of neuropeptide Y–like immunoreactivity (NPY-LI). After centrifugation at 4°C, plasma was removed and stored at −80°C until analyzed for catecholamines by high-performance liquid chromatography (HPLC)\textsuperscript{20} and NPY-LI by radioimmunoassay after acid ethanol extraction.\textsuperscript{21} Radiolabeled \textsuperscript{3}H\textsubscript{NE} was determined as described previously,\textsuperscript{22} with the modification that \textsuperscript{3}H activity was determined by scintillation counting.
counting of the fraction of the eluant from the cation-exchange HPLC column corresponding to NE. Thus, NE and [3H]NE were determined after the same chromatographic separation. Radioactivity in the [3H]NE fraction was used to calculate the clearance of NE from plasma, the fractional extraction of NE over the forearm, and the NE spillover rate into arterial plasma as described earlier.14,15 The net overflow of NE from the forearm was calculated using the brachial venoarterial plasma concentration difference for endogenous NE, the fractional extraction of [3H]NE in the tissue, and the plasma flow through the forearm.22

No major elimination of NPY-LI appears to occur during a single passage through skeletal muscle.22 Thus, the net overflow of NPY-LI from the forearm was calculated as the venoarterial plasma concentration difference multiplied by plasma flow in the forearm. Arterial blood was also collected for determination of felodipine concentrations. The blood was centrifuged and plasma kept frozen until analyzed. A gas chromatographic method with electron-capture detection was used.24 Felodipine analyses in plasma were performed at the Department of Bioanalytical Chemistry, Astra Hässle AB, Sweden.

Study Protocol

After insertion of the catheters, the subject was raised to the semirecumbent position, and equipment for measurement of FBF was attached. Infusion of [3H]NE was started, and the subject was left resting for 40 minutes. After this equilibration period, baseline measurements began. Arterial and venous blood samples were taken for neurohormonal analyses immediately before pressure measurements. Systemic arterial and pulmonary arterial blood pressures, heart rate, cardiac output, FBF, and right atrial pressure were recorded. Measurements were repeated during minutes 3 to 5 and during the minutes 9 to 11 of CWT. SAP and DAP were recorded continuously during CWT (except during arterial blood sampling) and up to 5 minutes after CWT. Cardiac output and FBF were also determined 4 to 6 minutes after CWT. Fifty minutes after termination of the first stress test, a continuous intravenous infusion of felodipine was started. The infusion rate was 10 mg/min during 20 minutes, after which the rate was reduced to 7.5 mg/min. After 45 minutes of felodipine infusion, resting measurements and the CWT with registrations as described above were repeated.

Eight of the hypertensive patients were reexamined after approximately 8 weeks (range, 6 to 13 weeks) of oral treatment with felodipine in an extended-release formulation (Plendil): 5 mg daily during the first week followed by 10 mg daily. None of the patients received any other medication during this time. The last felodipine tablet was taken between 2 and 3 hours before the second investigation was begun. On arrival in the laboratory the hypertensive patients were reexamined according to the procedure described above for the first CWT; ie, no intravenous felodipine was given, and only one stress test was performed.

Statistical Analyses

Results are presented as mean±SEM or ranges. Changes of median values are presented when responses were not normally distributed. Statistical evaluation was performed by repeated-meaasures ANOVA (SUPPERANOVA, Abacus Concepts Inc), which included the effects of felodipine and mental stress and comparisons between groups. The ANOVAs were performed on original data even if relative changes are given in the results. For anthropometric and baseline data, Student's t test for unpaired data (STATVIEW II, Abacus Concepts) was used. Resting values within groups before and after short-term or long-term treatment were compared by Student's t test for paired data or, when variables were not normally distributed, Wilcoxon's signed rank test for paired groups (STATVIEW II). A value of P<.05 was considered statistically significant.

Results

Before Treatment

Circulatory and sympathoadrenal characteristics and responses to mental stress in these patients and healthy control subjects before treatment have been reported previously.25 In short, baseline levels of SAP, DAP, SVR, and FVR were higher in the hypertensive patients than in the control subjects (Fig 1, Table 1). There were no differences between the groups with regard to baseline levels of catecholamines (Fig 2, Table 2). During mental stress the hypertensive patients showed significant increases of heart rate (+17 beats per minute [bpm]), SAP (+11%), DAP (+12%), stroke volume (+13%), cardiac output (+44%), and FBF (+140%) and decreases of SVR (−21%) and FVR (−49%) after 9 minutes of CWT, ie, during steady-state stress (Fig 1). NE spillover to arterial plasma (+63%) and NE overflow from the forearm (+150%) also increased (Fig 2). These responses were similar in the control group.

Acute Effects of Felodipine

Resting Values

Intravenous infusion of felodipine resulted in a mean plasma felodipine concentration of 10.5 (range, 8.7 to 13.1) nmol/L in the hypertensive group and 10.3 (7.6 to 16.3) nmol/L in the control group.

In the hypertensive group mean arterial pressure decreased by 8% (P<.01) because of a 22% reduction of SVR (P<.001). Heart rate increased by 10 bpm (16%) (P<.001) and cardiac output by 1.3 L/min (20%) (P<.01). There were no significant changes of stroke volume, pulmonary artery pressure, or right atrial pressure. FBF increased by 11.4 mL·min⁻¹·100  (40%) (P<.01) because of a 30% decrease of FVR (P<.001) (Fig 1, Table 1). Arterial and venous plasma NE concentrations increased (P<.01 and P<.001, respectively), and NE clearance from arterial plasma increased slightly but significantly (P<.05). Felodipine also induced marked increases of arterial NE spillover (+61%) and NE overflow from the forearm (+115%) (P<.001 for both). Arterial plasma epinephrine was unchanged (Fig 2, Table 2). There was a small increase of NPY-LI from 19.1±0.9 to 20.3±1.0 pmol/L (P<.05). The fractional extraction of tritiated NE was approximately 40% and was unchanged in response to felodipine.

In the control group mean arterial pressure decreased by 6% (not significantly less than in the hypertensive group). In contrast to findings in the hypertensive group, the control group demonstrated no significant effects of felodipine on resting FBF, FVR, or NE overflow from the forearm (P<.05, P<.01, and P<.01, respectively, compared with the hypertensive group). The reduction of SVR was less pronounced than in the hypertensive patients (P<.05) but still significant (P<.001). Right atrial pressure fell from 5.2 to 4.1 mm Hg (P<.05), in contrast to unchanged levels in the hypertensive group. Venous plasma NE increased (P<.001), but this response was less pronounced than in the hypertensive patients (P<.05). The small increase of NPY-LI from 16.8±1.4 to 17.6±1.6 pmol/L was not significant. Apart from this, the control subjects responded to felodipine in a manner similar to that of the hypertensive patients with regard to resting values (Table 2).
Mental Stress

ANOVA revealed no differences in stress reactivity between the groups, with the exception of FVR, which decreased by 47% in the control subjects and 33% in the hypertensive patients (P<.05 for group difference). Responses to mental stress before and after felodipine are therefore presented with the two groups combined for the remaining variables.

The heart rate response to mental stress was slightly amplified by intravenous felodipine (P<.001), from 17 to 20 bpm in the hypertensive patients and from 17 to 18 bpm in the control subjects. The SAP and DAP responses were attenuated (P<.001 and P<.01, respectively) because of less marked initial rises in pressure during stress. “Steady-state” responses, which are less prone to adaptation on repetition of CWT, were less affected (Fig 1). The stress-induced decreases of SVR (−8% in the hypertensive patients and −18% in the control subjects), which are highly reproducible after placebo administration, were smaller during intravenous felodipine (P<.05) (Fig 1). The increase of arterial epinephrine (60% in the hypertensive patients and 56% in the control subjects) was less pronounced during mental stress after felodipine (P<.01), as was the increase in NE clearance from arterial plasma (P<.05). The responses to mental stress of arterial and venous plasma NE, NE spillover to arterial plasma, and NE overflow from the forearm were unaffected by felodipine (Fig 2), as was the fractional extraction of [3H]NE. The small but significant increase of NPY-LI in response to mental stress persisted during felodipine, but the maximal increase occurred later during the stress.

Long-term Effects of Felodipine

Resting Values

The long-term effects of felodipine were evaluated in eight hypertensive patients. Their mean plasma concentration of felodipine at the time of investigation was 11.0 (2.9 to 20.4) nmol/L during long-term treatment. SAP and DAP had decreased further, by 7% (12 mm Hg) and 8% (9 mm Hg), respectively, compared with the short-term effect of the drug (P<.01 for both). This was related to the return of heart rate and cardiac output values to levels that were not significantly different from the basal levels, concomitant with a preserved reduction of SVR (Fig 3, Table 3). FBF returned to the pretreatment level, but FVR remained as low as in the acute situation (Fig 3, Table 3). Arterial NE levels, NE spillover rates, and NE overflow from the forearm remained as elevated as during the intravenous infusion of felodipine; arterial epinephrine levels were only slightly lower (Fig 4, Table 4).

Mental Stress

In this group (n=8), the reactions to mental stress after short-term administration of felodipine included an enhanced heart rate response (+21 bpm compared...
with +18 bpm before treatment, P<.05), an attenuated systolic pressor response (+8% versus +11%, P<.01), but an unchanged diastolic pressor response. The FVR response was attenuated (~39% versus ~53%, P<.01), but there was no significant effect on the stress reactivity of SVR (Fig 3). There were more marked increases of arterial plasma NE (P<.01) (Fig 4) and venous plasma NE (P<.05) but no changes of the stress responses of NE spillover to arterial plasma, NE overflow from the forearm, arterial NE clearance, arterial plasma epinephrine, or arterial NPY-LI after short-term administration of felodipine in these patients.

During long-term treatment FBF increased less (P<.05) in response to mental stress. FVR decreased

### Table 1. Hemodynamic Variables at Rest Before and During Intravenous Felodipine In Hypertensive Patients and Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Rest Before Felodipine</th>
<th>Rest During Felodipine (45 minutes)</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>HT</td>
<td>68±4</td>
<td>78±5*</td>
<td>+16±2</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>66±3</td>
<td>72±2†</td>
<td>+11±3</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>HT</td>
<td>8.0±0.7</td>
<td>9.3±0.6†</td>
<td>+20±4</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>7.4±0.3</td>
<td>8.4±0.5‡</td>
<td>+13±4</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>HT</td>
<td>118±6</td>
<td>121±5</td>
<td>+4±4</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>115±7</td>
<td>117±8</td>
<td>+2±4</td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>HT</td>
<td>178±7</td>
<td>164±4†</td>
<td>-7±2</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>130±3</td>
<td>123±3‡</td>
<td>-5±2</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>HT</td>
<td>111±3</td>
<td>101±2*</td>
<td>-8±2</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>78±2</td>
<td>72±2*</td>
<td>-7±1</td>
</tr>
<tr>
<td>SVR, U</td>
<td>HT</td>
<td>17.6±1.3</td>
<td>13.5±0.7*</td>
<td>-22±3</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>13.1±0.6</td>
<td>10.9±0.5*</td>
<td>-18±3</td>
</tr>
<tr>
<td>FBF, mL·L⁻¹·min⁻¹</td>
<td>HT</td>
<td>29.7±4.9</td>
<td>41.1±6.7†</td>
<td>+40±10</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>26.3±1.8</td>
<td>26.9±3.0</td>
<td>+2±10</td>
</tr>
<tr>
<td>FVR, U</td>
<td>HT</td>
<td>5.50±0.7</td>
<td>3.85±0.6*</td>
<td>-30±5</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>3.79±0.3</td>
<td>3.74±0.5</td>
<td>-1±10</td>
</tr>
</tbody>
</table>

HT Indicates hypertensive patients (n=11); C, control subjects (n=10); SAP, systolic brachial arterial pressure; DAP, diastolic brachial arterial pressure; SVR, systemic vascular resistance; FBF, forearm blood flow; and FVR, forearm vascular resistance. Values are mean±SEM.

*P<.001, †P<.01, ‡P<.05 vs basal values.

§P<.01, ¶P<.05, between groups.

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**Fig 2.** Line graphs show arterial plasma concentrations of norepinephrine (NE) and epinephrine (Epi), arterial NE spillover rate, and NE overflow from the forearm in response to mental stress (color word conflict test, CWT) before and during intravenous felodipine (felo) infusion. HT indicates hypertensive patients (n=11); C, control subjects (n=10). Values are means. Symbols as in Fig 1. For statistics, see the text and Table 2.
The hemodynamic responses to short-term administration of felodipine in the present study are in broad agreement with those previously reported (see Reference 26). Thus, the blood pressure reduction caused by reduced SVR is attenuated by rises in heart rate and cardiac output. The cardiac reaction is thought to be reflex in origin and primarily caused by unloading of the arterial baroreceptors. Evaluation of the entire baroreflex function, however, requires assessments also of sympathetic nerve activity to the resistance vessels of the systemic circulation, as the regulation of SVR is as important as adjustment of cardiac output in the control of arterial blood pressure. So far, the effects of calcium antagonists on this important efferent link of the arterial baroreflex have been only crudely assessed by determination of NE concentrations in peripheral venous plasma. The present data clearly show that sympathetic neural outflow to the systemic circulation is increased. The present data confirm and extend previous speculations that elevated venous plasma NE concentrations in response to short-term felodipine administration are caused by increased sympathetic activity. The isotope dilution method and both arterial and venous sampling used in the present study provide detailed information on systemic and local NE turnover and allow us to conclude that both systemic and forearm sympathetic nerve activity are increased. The present data clearly show that sympathetic neural outflow to the systemic circulation is elevated by calcium antagonist–induced vasodilatation, in accordance with activation of the arterial baroreflex. The present data clearly show that sympathetic neural outflow to the systemic circulation is elevated by calcium antagonist–induced vasodilatation, in accordance with activation of the arterial baroreflex. The present data confirm and extend previous speculations that elevated venous plasma NE concentrations in response to short-term felodipine administration are caused by increased sympathetic activity. The isotope dilution method and both arterial and venous sampling used in the present study provide detailed information on systemic and local NE turnover and allow us to conclude that both systemic and forearm sympathetic nerve activity are increased. The present data suggest that measurements of venous plasma NE concentrations underestimate the elevation of local nerve activity. Thus, NE overflow from the forearm increased considerably more than venous plasma NE levels during stress (and after felodipine in the hypertensive patients) because of the increase in plasma flow through the forearm. Increased "washout" of NE from the forearm during vasodilatation may

### Table 2. Norepinephrine and Epinephrine Data in Study Subjects at Rest and During Mental Stress Before and During Intravenous Felodipine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Untreated Rest</th>
<th>CWT (9 minutes)</th>
<th>Felodipine Rest</th>
<th>CWT (9 minutes)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial plasma NE, nmol/L</td>
<td>HT</td>
<td>1.91±0.17</td>
<td>2.51±0.27</td>
<td>2.70±0.28</td>
<td>3.75±0.43</td>
<td>f†</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1.71±0.13</td>
<td>2.32±0.20</td>
<td>2.26±0.17</td>
<td>2.94±0.29</td>
<td>s†</td>
</tr>
<tr>
<td>Venous plasma NE, nmol/L</td>
<td>HT</td>
<td>1.90±0.15</td>
<td>2.38±0.24</td>
<td>2.88±0.22</td>
<td>3.57±0.26</td>
<td>f†</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1.79±0.13</td>
<td>2.28±0.14</td>
<td>2.33±0.19</td>
<td>2.95±0.30</td>
<td>s†</td>
</tr>
<tr>
<td>Arterial plasma Epi, nmol/L</td>
<td>HT</td>
<td>0.35±0.09</td>
<td>0.55±0.08</td>
<td>0.35±0.06</td>
<td>0.52±0.11</td>
<td>s§</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.37±0.06</td>
<td>0.64±0.11</td>
<td>0.41±0.07</td>
<td>0.60±0.09</td>
<td>fxs§</td>
</tr>
<tr>
<td>Arterial NE spillover, L·min⁻¹·m⁻²</td>
<td>HT</td>
<td>2.41±0.22</td>
<td>3.98±0.48</td>
<td>3.87±0.41</td>
<td>5.86±0.66</td>
<td>f†</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2.30±0.23</td>
<td>3.67±0.39</td>
<td>3.26±0.42</td>
<td>4.45±0.60</td>
<td>s†</td>
</tr>
<tr>
<td>Arterial NE clearance, pmol·min⁻¹·L⁻¹</td>
<td>HT</td>
<td>1.27±0.05</td>
<td>1.59±0.11</td>
<td>1.44±0.09</td>
<td>1.56±0.12</td>
<td>s†</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1.33±0.07</td>
<td>1.56±0.04</td>
<td>1.40±0.08</td>
<td>1.48±0.08</td>
<td>fxs§</td>
</tr>
<tr>
<td>NE overflow from forearm, pmol·min⁻¹·L⁻¹</td>
<td>HT</td>
<td>13.6±1.89</td>
<td>34.1±5.21</td>
<td>27.7±3.80</td>
<td>49.5±8.89</td>
<td>f†</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>11.8±1.75</td>
<td>23.2±3.65</td>
<td>14.7±2.53</td>
<td>43.4±9.01</td>
<td>s†</td>
</tr>
</tbody>
</table>

CWT indicates color word conflict test; NE, norepinephrine; HT, hypertensive patients (n=11); C, control subjects (n=10); and Epi, epinephrine. In the ANOVA column, f indicates effects of felodipine; s, effects of mental stress; g, group differences (hypertensive vs control); fxs, effects of felodipine on stress reaction; and fxs, group differences with felodipine. *P<.05, †P<.01, ||P<.05, for differences between groups regarding only the effects on resting values.

*P<.05, †P<.01, ||P<.05, for differences between groups regarding only the effects on resting values.
FIG 3. Line graphs show hemodynamic responses to mental stress (color word conflict test, CWT) in hypertensive patients (HT, n=8) before (filled symbols, solid lines) and during (filled symbols, broken lines) intravenous felodipine (felo) Infusion and during long-term felodipine treatment (open symbols, dotted lines). Values are means. For statistics, see the text and Table 3.

I contribute to the enhanced regional NE overflow, but this does not explain the present findings. 25 Our results thus show that forearm sympathetic nerves participate in the general sympathetic counterregulation when blood pressure is lowered with felodipine in hypertensive patients.

The effects of long-term felodipine treatment were assessed at plasma concentrations that were similar to those obtained in the short-term experiments; our short- and long-term results are therefore comparable. Long-term treatment with felodipine resulted in a further decrease of mean arterial pressure compared with the short-term intravenous administration, as SVR (and FVR) remained depressed and cardiac output and heart rate returned toward pretreatment values. These long-term hemodynamic effects of felodipine are in agreement with earlier results. 26-29 Plasma NE levels and spillover, as well as NE overflow from the forearm, remained as elevated as during the felodipine infusion. The further lowering of blood pressure during long-term treatment might have had some influence. However, there was no major adaptation with regard to sympathetic outflow within the time frame for the present study, ie, 2 months.

Some investigators 11 have claimed the long-term readjustment of heart rate to be due to resetting of the baroreflex to a lower pressure, whereas others 10 12 have interpreted persistently elevated venous plasma NE concentrations as contrary to this mechanism. Since the arterial baroreflex controls arterial blood pressure by adjusting both cardiac output and SVR, it is not adequate to base conclusions regarding its function on heart rate data only. The baroreflex control of heart rate is clearly reset, which may be due to decreased cardiac sympathetic activity, increased vagal activity, or both. Spectral analysis of heart rate variability in postinfarction patients has not revealed signs of elevated cardiac sympathetic activity after 1 week of treatment with the dihydropyridine calcium antagonist nifedipine. 30 Reduced cardiac β-adrenergic receptor sensitivity is a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Felodipine</th>
<th>During IV Felodipine</th>
<th>During Long-term Felodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>72±5</td>
<td>83±5*</td>
<td>74±4</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>8.4±0.9</td>
<td>9.8±0.8†</td>
<td>8.8±0.8</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>117±8</td>
<td>121±7</td>
<td>121±9</td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>175±5</td>
<td>166±4†</td>
<td>154±5*</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>110±3</td>
<td>103±3†</td>
<td>95±2*</td>
</tr>
<tr>
<td>SVR, U</td>
<td>16.8±1.5</td>
<td>13.0±0.7†</td>
<td>13.6±1.0†</td>
</tr>
<tr>
<td>FBF, mL - L⁻¹·min⁻¹</td>
<td>29.5±6.7</td>
<td>36.7±9.3†</td>
<td>29.5±3.9</td>
</tr>
<tr>
<td>FVR, U</td>
<td>5.8±0.9</td>
<td>4.4±0.8†</td>
<td>4.5±0.7†</td>
</tr>
</tbody>
</table>

Variable definitions are as in Table 1. Values are mean±SEM.

*P<.001, †P<.01, ‡P<.05, baseline vs treatment (IV and long-term).

§P<.01, IV vs long-term.
possible explanation for the adaptation of heart rate, but this seems less likely in view of the preserved cardiac response to stress. NE overflow from the heart was not investigated in the present study, but sympathetic activation in response to stress is nonuniform and preferentially involves the renal and cardiac sympathetic outflows. The renal contribution to NE in arterial plasma is considerably greater than the cardiac contribution (see Reference 13). Long-term adaptation to blood pressure-lowering treatment could also be nonuniform and involve reduced cardiac sympathetic activity with little influence on arterial NE without similar adaptation elsewhere. Our data suggest that the efferent vasoconstrictor limb of the arterial baroreflex is not reset.

Sympathoadrenal activity is also influenced by cardio-pulmonary reflexes. However, this does not seem to explain our findings because right atrial and pulmonary arterial pressures were unaffected by felodipine treatment in the hypertensive patients. A diuretic action of long-term felodipine treatment might have contributed to the elevated total sympathetic activity. However, in hypertensive patients treated with a diuretic (chlorothalidone), the elevated plasma levels of NE emanated mainly from the kidneys. The signs of increased sympathetic activity in the forearm found in the present study could not be explained by this mechanism.

Although the plasma concentrations of felodipine were the same in the short- and long-term experiments, it could be argued that oral treatment results in fluctuating plasma levels of felodipine, leading to iterated intermittent activation of the baroreflex caused by variations in blood pressure and resulting in repeated increases in heart rate and venous plasma NE levels, as shown by Leenen and Hollis. However, this is unlikely in the present study for two reasons: first, we

### Table 4. Norepinephrine and Epinephrine Data in Eight Hypertensive Patients at Rest and During Mental Stress, Untreated, During Intravenous Felodipine, and During Long-Term Treatment With Felodipine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Untreated</th>
<th>IV Felodipine</th>
<th>Long-term Felodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>CWT (9 minutes)</td>
<td>Rest</td>
</tr>
<tr>
<td>Arterial plasma NE, nmol/L</td>
<td>1.82±0.23</td>
<td>2.31±0.34*</td>
<td>2.43±0.30†</td>
</tr>
<tr>
<td>Venous plasma NE, nmol/L</td>
<td>1.85±0.20</td>
<td>2.22±0.31</td>
<td>2.65±0.25†</td>
</tr>
<tr>
<td>Arterial plasma Epl, nmol/L</td>
<td>0.39±0.12</td>
<td>0.61±0.10*</td>
<td>0.37±0.08</td>
</tr>
<tr>
<td>Arterial NE spillover, nmol·min⁻¹·m⁻²</td>
<td>2.22±0.27</td>
<td>3.44±0.53*</td>
<td>3.48±0.48†</td>
</tr>
<tr>
<td>Arterial NE clearance, L·min⁻¹·m⁻²</td>
<td>1.23±0.06</td>
<td>1.50±0.11*</td>
<td>1.42±0.11§</td>
</tr>
<tr>
<td>NE overflow from forearm, pmol·min⁻¹·L⁻¹</td>
<td>13.3±2.4</td>
<td>34.7±5.9*</td>
<td>25.6±4.8†</td>
</tr>
</tbody>
</table>

Definitions are as in Table 2. Values are mean±SEM.
**P<.01 for stress reactions in untreated patients.
†P<.001, †P<.01, †P<.05, compared with untreated baseline.
*P<.01, ‡P<.05, change in stress reactivity compared with untreated.
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used an extended-release formulation with a smooth plasma concentration profile over 24 hours, and second, the normalization of heart rate during long-term treatment is not compatible with "subacute" activation of the arterial baroreflex. The observed elevation of NE spillover is therefore not a temporary effect in response to each felodipine administration but a sign of constantly raised sympathetic activity. Our results are in agreement with those of an earlier study using the same treatment (extended-release felodipine) and venous plasma NE concentration measurements.10

The hemodynamic and sympathoadrenal responses to felodipine were similar in the hypertensive and control groups. The only striking difference between the groups was that FVR and regional sympathetic activity were greater forearm vascular sensitivity than normotensive phases18; this is a likely explanation for the attenuation of adaptation to the test may occur during its initial rate response slightly, whereas the initial pronounced effect on flow resistance for a given change in this study. Third, abnormalities in the cell membranes and their transport systems in hypertension39 might influence the sensitivity toward calcium antagonism. Hypertensive patients have also been shown to have a greater forearm vascular sensitivity than normotensive subjects to another calcium antagonist, verapamil.40 The latter study was performed with brachial intra-arterial infusions, which eliminate reflexogenic components in the response. Thus, hypertensive patients may be hyper-responsive to certain vascular effects of calcium antagonism.

Responses to mental stress before treatment in the present study have been discussed in detail elsewhere.25 Stress reactivity was similar in hypertensive patients and normotensive subjects. Hemodynamically, mental stress elicits the so-called defense reaction described above. There were also increases in arterial plasma NE and epinephrine, NE spillover to arterial plasma, and NE overflow from the forearm, indicating increased sympathoadrenal activity, systemically and regionally. Short-term felodipine administration augmented the heart rate response to stress slightly, whereas the initial pressor response was somewhat attenuated; the sympathetic response was essentially unchanged. Some degree of adaptation to the test may occur during its initial phases18; this is a likely explanation for the attenuation of pressor responses, as "steady-state" responses to CWT were less affected. The plasma epinephrine response was also slightly attenuated. After 2 months of treatment, stress reactivity was similar to that seen after short-term administration of felodipine in these patients with regard to both hemodynamic and sympathoadrenal responses. The "defense reaction" is thus preserved, although at a lower arterial pressure level, which might be of functional importance. Preserved hemodynamic responses to mental stress during long-term treatment with a calcium antagonist have also been found in a previous noninvasive study.41

In conclusion, vasodilatation induced by a vascularly selective calcium antagonist lowers blood pressure and elicits reflexogenic sympathetic counterregulation both systemically (NE spillover to arterial plasma) and in the forearm (local NE overflow). Interestingly, this sympathetic activation persists during long-term treatment. The therapeutic implications of these findings are unknown, but sympathetic activity may influence the vascular adaptation to antihypertensive treatment.14 Heart rate and cardiac output returned toward baseline levels during long-term treatment, suggesting readaptation of autonomic nervous influences on the heart. The sympathetic vasoconstrictor limb of the arterial baroreflex, on the other hand, seems to remain activated over a longer period of time. Regional changes in sympathetic activity over time during treatment with calcium antagonists thus deserve greater attention.

Acknowledgments

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