Cardiovascular and neurohumoral postural responses and baroreceptor abnormalities during a course of adjunctive vasodilator therapy with felodipine for congestive heart failure

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ABSTRACT Studies in patients with congestive heart failure (CHF) have demonstrated an abnormal β-adrenergic reflex vasodilation during orthostatic tilt. Baroreflex modulation of vascular resistance in patients with CHF was investigated during therapy with a vasoselective calcium antagonist, felodipine. Eight patients on conventional therapy for severe CHF were studied after a 3 week course of additional felodipine or placebo treatment under randomized, double-blind, and crossover conditions. Forearm subcutaneous vascular resistance (FSVR) was estimated with use of the local 133Xe washout. Aortic pulsatile stretch, expressed as the systolic distension in percent of diastolic diameter, was calculated from echocardiographic measurements of aortic root diameters. At 3 weeks, felodipine reduced the arterial pressure, systemic vascular resistance, and FSVR, preserved cardiac filling pressures and heart rate, and increased cardiac output, stroke volume, and aortic pulsatile stretch. Upright tilt (45 degrees) was used to study baroreflex-mediated cardiovascular responses. The unloading of cardiopulmonary baroreceptors during upright tilt was substantial and about equal during both treatment courses, but the pulse pressure was maintained during the placebo and decreased during the felodipine period. During tilt, the patients on placebo failed to increase heart rate and their FSVR, systemic vascular resistance, and arterial mean pressure were decreased, whereas during tilt after felodipine, heart rate and systemic vascular resistance increased to maintain arterial mean pressure and FSVR also tended to increase. Both the stroke volume and aortic pulsatile stretch increased during tilt in patients on placebo but they decreased in those on felodipine. The tilt caused increments in circulating norepinephrine and epinephrine levels during both treatment regimens. Regulation of FSVR during the sympathetic stimulation of orthostatic stress was further elucidated. Proximal neural blockade caused an increase in FSVR during tilt in patients on placebo and a decrease in FSVR during tilt in those on felodipine. Local β-adrenoceptor blockade caused similar increments in FSVR during tilt in patients on both treatments. Combined proximal and local blockade still increased FSVR during tilt in those on placebo, but caused no change in FSVR during tilt in those on felodipine. This study demonstrates that felodipine normalizes baroreflex control of vascular resistance in patients with CHF. It seems unlikely that this is caused by a nonspecific effect of a vasodilator or an effect on the mechanical stimulus to baroreceptors; it is probably due instead to sensitization of cardiopulmonary and arterial baroreceptors by this calcium antagonist.


VAGAL AND GLOSSOPHARYNGEAL afferents from cardiopulmonary and arterial baroreceptors exert a restraint on the medullary vaspressor center that tonically regulates the sympathetic efferent outflow to the heart and peripheral circulation.1-2 Loading of the baroreceptors during augmentation of cardiac filling would increase their afferent restraint and reflexly reduce sympathetic efferent activity.3 Unloading of the baroreceptors during orthostatic tilt would activate the baroreflexes and elicit a regulated increment in heart rate and vascular resistance to maintain the arterial pressure.1-3 The human forearm has been used to study baroreflex-mediated vasoconstriction during upright tilt1-4,5 and the regional distribution of this vasoconstriction in subcutaneous and skeletal muscle vascular beds.6 Evidence from these studies has suggested that

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the arterial baroreflex is augmented in the upright posture,1,4 that the cardiopulmonary baroreflex plays an important part in regulation of the vasomotor tone in forearm vascular beds,1,5,6 and that subcutaneous vascular resistance is selectively modulated by the cardiopulmonary baroreflex.6

Patients with congestive heart failure (CHF) have been demonstrated to have reduced cardiac responsiveness to sympathetic efferent activity,7,8 and attenuated cardiovagal efferent control9 and autonomic control of the heart may thus be absent.10 In contrast to individuals receiving cardiac transplants,10 patients with CHF have been observed to have neurohumoral excitation11-13 and increased cardiac pressures and dimensions relating to ultrastructural changes in the myocardium.14 Degenerative changes in human arterial15 and animal cardiopulmonary16 baroreceptor afferent endings have been noted in studies of heart failure. The animal studies have also reported reduced afferent activity from cardiopulmonary receptors16,17 and impaired efferent control of arterial and cardiopulmonary baroreflexes.18 Reduced baroreceptor afferent restraint has recently been suggested to modify a β-adrenergic reflex mechanism operating during upright tilt in both subcutaneous19 and skeletal muscle20 vascular beds in patients with severe CHF.

Few data are available regarding the effects of vasodilator therapy on autonomic control mechanisms in CHF,21 although such therapy has been increasingly used in the management of patients. Currently available calcium antagonists have vasodilator and negative inotropic properties.22 Felodipine, a new calcium antagonist with a pronounced vascular selectivity,23 has been shown to exert sustained hemodynamic efficacy in patients with CHF.24

The present study was undertaken to test the hypothesis that effects of felodipine therapy on baroreceptor mechanisms in CHF are an important reason for the clinical efficacy of such a therapy. Cardiovascular responses to upright tilt in patients with severe CHF were assessed during a 3 week course of adjunctive felodipine treatment under placebo-controlled conditions.

Methods

Patient selection and study design. Eight patients from 47 to 65 (mean 54.5) years old were selected because they had severe CHF (New York Heart Association functional class III) while on treatment with digoxin and diuretics. They all had severe left ventricular myocardial dyssynergy, as disclosed by angiographic studies performed 1 to 2 months before our study. Their left ventricular end-diastolic and end-systolic volumes were abnormally augmented and ejection fraction ranged from 14% to 29%. Baseline assessment was carried out 2 weeks before randomization and digoxin and diuretic regimens were optimally set. Medications were continued unchanged and patients entered the study 2 weeks later if they were clinically stable and had normal blood counts, electrolytes, and therapeutic serum levels of digoxin. They were randomly assigned in a double-blind fashion to treatment with felodipine, 10 mg twice daily, or with matching placebo tablets. After 3 weeks of therapy, the patients were hemodynamically investigated, and the next day they crossed over to the second 3 week period of therapy under double-blind conditions. The hemodynamic investigations were repeated at the end of the second treatment period. The study protocol was approved by the official ethical committee in Copenhagen. Informed consent was obtained from each patient.

Procedures. The hemodynamic investigations were carried out twice in each patient at the end of a 3 week treatment period with either felodipine or placebo. The compliance of patients was checked by determination of plasma levels of trial drug. Careful clinical assessments of patients were carried out the day before the hemodynamic studies and ensured that they had normal blood counts and electrolytes. The hemodynamic measurements were started 2 hr after administration of the trial drug and baseline therapy.

Central hemodynamic measurements. All catheter procedures were performed under fluoroscopic control. A balloon-tipped triple-lumen thermodilution catheter (Gould SP 1435) was placed in the pulmonary artery for pressure measurements and determination of cardiac output (dilution curves of five consecutive measurements were recorded). All pressures were recorded with Statham P23Db transducers. Supine hemodynamics were measured after patients had rested 1 hr on a tilt table. Thereafter, the patients were passively and slowly (within 1 min) tilted to a 45 degree angle with the feet supported by a base platform, and hemodynamic measurements were repeated within 5 to 10 min after initiation of tilt. All pressures were measured with reference to the midaxillary level while patients were supine and with reference to the right atrial level individually set for each patient during tilt. Arterial blood pressure was measured by cuff and mercury column sphygmomanometer. Concordance between the left ventricular end-diastolic and pulmonary capillary wedge pressures and between the aortic and arm blood pressures had previously been established in these patients while in the supine and tilted positions. Systemic vascular resistance (dynes-sec-cm⁻⁵) was calculated as 80 × (mean arterial pressure minus right atrial pressure) / cardiac output.

Vascular hemodynamic measurements. Echocardiographic measurements of aortic root dimensions were obtained with a phased-array scanner (Aloca SSD-800). An M mode scan of the aortic root was recorded while patients rested supine and 5 to 10 min after initiation of 45 degree upright tilt, as described above. Aortic diameters were measured as the distance (mm) between the leading edges of the anterior and posterior aortic wall, at diastole (R wave on the electrocardiogram), and at systole (peak anterior motion of anterior wall).25 Aortic pulsatile stretch was calculated as the systolic distension in percent of diastolic diameter of the aortic root.

Forearm subcutaneous blood flow was measured by the local ¹³³Xe-washout technique.26 Measurements were begun 1 hr after patients had been resting supine on a tilt table at a room temperature constantly kept at 22°C. Via a thin cannula, 0.1 ml (1 mCi) of ¹³³Xe (Radiochemical Centre, Amersham, U.K.) dissolved in saline and mixed with 0.1 ml of saline was injected subcutaneously into the skin covering the left brachioradial muscle. An equal deposit of ¹³³Xe solution was mixed with 0.1 ml (10 ng) of propranolol solution in saline (0.1 mg/liter) and injected at a corresponding site on the right forearm. Measurements were started 30 min after the subcutaneous injections to avoid influences of the injection trauma on the washout rate of
The y-radiation of 133Xe was measured by NaI (TI) scintillation detectors placed perpendicular to the site of injection at a distance of about 15 cm. Care was taken that the counting geometry remain constant during a single investigation. The recorded activity was fed to a universal printing gamma spectrometer (Novo Diagnostic System) with a window of acceptance adjusted around the 81 keV photopeak of 133Xe. The count rates were printed out every 5 sec without time delay.

Investigations consisted of two triads of measurements simultaneously obtained from both forearms, with each part of the trial lasting 5 to 10 min. Measurements were made as follows for each triad: (1) reference level (ref1; supine position with forearms at midaxillary lines), (2) test level (test; upright tilt as described above with forearms kept at heart level), (3) return to reference level (ref2). Proximal neural blockade was induced by subcutaneous infiltration of 2% lidocaine (without vasoconstrictant) in a V-shaped area 5 to 10 cm proximal, lateral, and medial to the studied area of forearms. About 10 min after this neural blockade, anesthesia and analgesia corresponding to the labeled field were confirmed on each side. The two triads of measurements described above were repeated about 10 min after the neural blockade.

Blood flow in subcutaneous tissue as determined by the local isotope washout technique can be calculated according to Kety27 as f (ml/min/100 g) = λ ⋅ k/100, where λ is the tissue-to-blood partition coefficient (ml/g) and k is the fractional washout rate constant per minute. The λ value was not determined in the present study, but since investigations on a particular day were performed with the use of the same radioactive depot, λ was assumed to remain constant during the different test conditions. Since 133Xe washout follows a monoeponential course, k was calculated from the regression analysis (least squares method) of the count rates transformed logarithmically and corrected for background activity.

Relative subcutaneous blood flow under test conditions was calculated as ftest / fref = ktest / kref, where ktest is the washout rate constant obtained during test conditions and kref is the average value of kref1 and kref2. To avoid variations in relative subcutaneous blood flow due to mechanisms other than the test, data were analyzed only when k at ref1 and ref2 did not differ more than 50%.

Relative subcutaneous vascular resistance was calculated from the measured relative blood flow and mean arterial and venous pressures. Forearm subcutaneous vascular resistance (FSVR) is expressed in arbitrary units (mm Hg-min/10−3) and was calculated as FSVR = ΔP / (k ⋅ 103), where ΔP is the mean perfusion pressure (Pv − Pp) in the forearm. Mean arterial pressure (Pm) was calculated as diastolic pressure + 1/3 (pulse pressure). Mean venous pressure (Pv) was taken as the mean right atrial pressure.

Determination of plasma concentrations of catecholamines. Venous plasma levels of norepinephrine and epinephrine were determined as previously described18 in patients in the supine position (1 hr rest) and within 5 to 10 min of upright tilt. Normal resting levels of norepinephrine and epinephrine were 0.4 to 1.9 and 0.07 to 0.44 nmol/liter, respectively.

Protocol. Cardiovascular dynamics were measured as described above in the eight patients at the end of each treatment period with felodipine or placebo. The peripheral and central hemodynamic measurements were carried out during the morning hours of two successive days at a room temperature of 22° C. Both measurements were started after a 1 hr rest period during which the patients were familiarized with the techniques. The sequence of the hemodynamic investigations was of the same order in each patient during both of the 3 week periods of treatment.

Statistics. The results are given as the mean ± SEM. The Wilcoxon signed-rank test was used. A .05 level of significance was assumed.

Results

Five patients started treatment with felodipine and three patients were started on placebo. The drug was well tolerated by all eight patients. Each patient received his or her usual dosages of digoxin and diuretics and had normal blood counts and electrolytes during both treatment periods. Plasma levels of felodipine were undetectable during the eight placebo periods and within the therapeutic range during periods of treatment with felodipine.

Supine cardiovascular dynamics. Table 1 compares the cardiovascular effects of felodipine after 3 weeks of therapy to those of placebo in the eight patients. Felodipine decreased the afterload, as evidenced by the reductions in mean arterial pressure (12%) and systemic vascular resistance (27%). Felodipine did not affect heart rate or the right or left ventricular filling pressures. Its afterload-reducing properties led to a substantial increment in the stroke volume (33%) that subsequently increased the cardiac index (22%). The drug induced a relative decrease in forearm subcutaneous vascular resistance of about 30% under supine reference conditions. Despite the lowered mean arterial pressure and maintenance of arterial pulse pressure during felodipine therapy, the aortic diastolic diameter

| TABLE 1 | Mean (±SEM) supine cardiovascular dynamics after 3 weeks of adjunctive treatment with felodipine or placebo in each of the eight patients with CHF |
|----------|-------------------------------------------------|-----------------|----------------|----------------|----------------|----------------|----------------|
|          | Placebo                                    | Felodipine      | p value <sup>a</sup> |
| HR (beats/min) | 85 (2)                                      | 80 (2)          | NS             |
| MAP (mm Hg)     | 97 (4)                                      | 85 (3)          | .01            |
| APP (mm Hg)     | 42 (3)                                      | 43 (3)          | NS             |
| RAP<sub>m</sub> (mm Hg) | 6 (1)                                      | 6 (1)           | NS             |
| PCWP<sub>m</sub> (mm Hg) | 22 (2)                                      | 18 (2)          | NS             |
| CI (l/min/m<sup>2</sup>) | 2.3 (0.1)                                  | 2.8 (0.2)       | .05            |
| SVI (ml/m<sup>2</sup>) | 27 (2)                                      | 36 (2)          | .02            |
| SVR (dynes-sec-cm<sup>-2</sup>) | 1720 (100)                                 | 1258 (80)       | .01            |
| FSVR (units)    | 20 (2)                                      | 14 (2)          | .01            |
| AoD-D (mm/m<sup>2</sup>) | 16.2 (0.3)                                 | 16.1 (0.3)      | NS             |
| AoD-S (mm/m<sup>2</sup>) | 16.7 (0.3)                                 | 17.2 (0.4)      | .05            |
| AoPS (%)        | 3.1 (0.3)                                   | 6.9 (1.0)       | .01            |

<sup>a</sup>Felodipine vs placebo.
did not decrease. However, felodipine increased the aortic systolic diameter and induced a twofold increment in aortic pulsatile stretch.

Cardiovascular responses to upright tilt. Figures 1 through 3 and table 2 summarize the cardiovascular responses to upright tilt during the placebo (P) and felodipine (F) treatment periods.

During upright tilt in patients on placebo, right and left ventricular filling pressures were reduced by 5 ± 1 and 10 ± 2 mm Hg, respectively, heart rate failed to increase, and systemic vascular resistance decreased by 380 ± 100 dynes-sec-cm⁻⁵ (figure 1). Mean arterial pressure decreased by 13 ± 2 mm Hg and cardiac index, stroke volume index, and aortic pulsatile stretch increased by 0.3 ± 0.1 liter/min/m², 4.8 ± 0.7 ml/m², and 5.0 ± 0.6%, respectively (figure 2). The aortic diastolic diameter was maintained despite the reduction in mean arterial pressure and maintenance of pulse pressure, but the aortic systolic diameter, and thereby the pulsatile stretch (table 2), was substantially increased. Forearm subcutaneous blood flow increased by 34 ± 7% (p < .01), corresponding to a decrease in forearm subcutaneous vascular resistance of 30 ± 5% (figure 3).

During upright tilt in patients on felodipine, the same patients had reduced right and left ventricular filling pressures (by 5 ± 1 and 7 ± 1 mm Hg, respectively) and increased heart rate (by 5 ± 1 beats/min) and systemic vascular resistance (by 120 ± 30 dynes-sec-cm⁻⁵; figure 1). The mean arterial pressure and cardiac index were maintained, but both the stroke volume index and aortic pulsatile stretch decreased by 2.2 ± 0.3 ml/m² and 3.3 ± 0.9%, respectively (figure 2). There was a reduction in arterial pulse pressure and no substantial change in the aortic diameters, but a decrease in the pulsatile stretch (table 2). Subcutaneous blood flow decreased by 16 ± 4% (p = .10), corresponding to an increment in forearm subcutaneous vascular resistance of 15 ± 5% (figure 3).

Changes in plasma catecholamine levels. As shown in table 3, felodipine increased supine plasma levels of norepinephrine but not those of epinephrine in the patients who had abnormally high plasma levels of both catecholamines. During tilt, the levels of norepinephrine and epinephrine in these patients increased by 33% and 15%, and 32% and 17%, respectively, while on placebo and felodipine.

Regulation of FSVR during upright tilt. About 10 min

**FIGURE 1.** Individual changes in cardiac filling pressures, heart rate, and systemic vascular resistance in patients with CHF moved from a supine to an upright tilted position at 3 weeks after adjunctive therapy with placebo (P) or felodipine (F). Points with bars denote the mean ± 2 SEM.
after the injection of lidocaine, anesthesia and analgesia corresponding to the labeled field were present. This proximal neural blockade in the control forearm caused average reductions in reference forearm subcutaneous vascular resistance of about 15% and 10% during the placebo and felodipine periods, respectively. As shown in figure 4, the neural blockade reversed the vasodilator response to upright tilt during the placebo period but induced vasodilation during tilt in patients on felodipine: blood flow decreased by 31 ± 6% (p < .01), corresponding to an increase in forearm subcutaneous vascular resistance of 30 ± 5%, during tilt on placebo, whereas blood flow increased by 35 ± 8% (p < .01), corresponding to a decrease in forearm subcutaneous vascular resistance of 22 ± 6%, during tilt on felodipine.

Local β-adrenergic blockade with propranolol caused a vasoconstrictor response to upright tilt during both placebo and felodipine periods (figure 5): blood flow decreased by 32 ± 6% (p < .01) and 28 ± 4% (p < .01), corresponding to increments in forearm subcutaneous vascular resistance of 29 ± 6%, and 28 ± 5% during tilt on placebo and felodipine, respectively. Additional proximal neural blockade in the right forearm caused average reductions in reference forearm subcutaneous vascular resistance of 16% during the placebo and 12% during the felodipine period. As shown in figure 6, the combined local β-adrenergic and proximal neural blockades caused substantially different vascular responses in the tilted position during the two treatment periods: with placebo, blood flow decreased by 35 ± 6% (p < .01), corresponding to an increase in forearm subcutaneous vascular resistance of 33 ± 6% (p < .01), while with felodipine, the relative changes were +1 ± 2% in blood flow and +8 ± 2% in forearm subcutaneous vascular resistance; both responses are insignificant.

**Discussion**

The patients on conventional therapy for severe CHF responded to afterload reduction with the selective vasodilator calcium antagonist felodipine with a preferential increment in the stroke volume and subsequently increased cardiac output. Cardiac filling pressures were preserved during adjunctive felodipine therapy; they decreased substantially during upright tilt and to a similar extent during treatment with felodipine and that with placebo. Despite the equal level of reflex stimulation to cardiopulmonary baroreceptors, the observed cardiovascular responses to upright tilt...
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FIGURE 3. Individual relative changes in forearm subcutaneous vascular resistance (%) caused by upright tilt during the two treatment courses in patients with CHF.

were widely different in the same patient during the two treatment courses: in contrast to placebo, felodipine induced reductions in the stroke volume, arterial pulse pressure, and aortic pulsatile stretch and increments in the systemic vascular resistance and heart rate, while the mean arterial pressure was maintained. Although the tilt-induced increment in forearm subcutaneous vascular resistance was attenuated during felodipine therapy as compared with that usually observed in normal subjects, it was substantially different from the subcutaneous vasodilation observed during tilt in individuals on placebo.

This study demonstrates that felodipine therapy restores reflex vasoconstrictor responses to upright tilt in patients with CHF. We propose that this is due to possible direct effects of the drug on baroreceptors, effects that influence the reflex control of forearm subcutaneous vascular resistance and systemic vascular resistance.

The restoration of reflex vasoconstrictor responses to upright tilt during felodipine therapy could reflect a

TABLE 2
Mean (± SEM) arterial pressures, aortic root dimensions, and pulsatile stretch during 45 degree upright tilt in eight patients with CHF during the placebo and felodipine treatment periods

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>p value</th>
<th>Felodipine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>84 (3)</td>
<td>.01</td>
<td>86 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>APP (mm Hg)</td>
<td>42 (3)</td>
<td>NS</td>
<td>38 (3)</td>
<td>.05</td>
</tr>
<tr>
<td>AoD-D (mm/m²)</td>
<td>16.1 (0.4)</td>
<td>NS</td>
<td>16.5 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>AoD-S (mm/m²)</td>
<td>17.4 (0.4)</td>
<td>.01</td>
<td>17.1 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>AoPS (%)</td>
<td>8.1 (0.6)</td>
<td>.01</td>
<td>3.6 (0.8)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Abbreviations are as in table 1.

*tilt vs supine.

FIGURE 4. Effects of proximal neural blockade on the tilt-induced relative changes in forearm subcutaneous vascular resistance during the two treatment courses in patients with CHF.

TABLE 3
Mean (± SEM) plasma levels of catecholamines in patients in the supine and tilted positions during the placebo and felodipine treatment periods (n = 8 patients with CHF)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Felodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (nmol/l)</td>
<td>3.9 (0.8)</td>
<td>5.3 (1.2)*</td>
</tr>
<tr>
<td>Epinephrine (nmol/l)</td>
<td>1.24 (0.24)</td>
<td>1.28 (0.22)</td>
</tr>
<tr>
<td>Supine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>5.2 (1.1)*</td>
<td>1.42 (0.20)c</td>
</tr>
<tr>
<td>Felodipine</td>
<td>7.0 (1.3)*</td>
<td>1.50 (0.22)c</td>
</tr>
</tbody>
</table>

*p < .05, felodipine vs placebo; b p < .05, tilt vs supine; c p < .02, tilt vs supine.
nonspecific effect of a vasodilator and improvement in the heart failure state. Hemodynamic improvement in patients with CHF during adjunctive vasodilator therapy with the converting-enzyme inhibitor captopril has been observed to be accompanied by the absence of reflex increments in vascular resistance and heart rate during upright tilt and by orthostatic hypotension.21 No data are available regarding effects of other vasodilators, such as hydralazine or nitrates, on reflex regulation of vascular tone in patients with heart failure. Studies in normal animals have demonstrated that, in addition to their vascular effects, calcium antagonists have important autonomic effects. Lowering of the extracellular calcium concentration has been shown to decrease threshold and augment sensitivity of arterial baroreceptors.28,29 Both diltiazem and verapamil have been reported to attenuate arterial baroreceptor sensitivity,30-32 whereas nifedipine has been shown to potentialize the activity of these receptors.32 Studies in man have shown that nifedipine can sensitize arterial and cardiopulmonary baroreceptors in normal subjects33 and reset and sensitize arterial baroreceptors in hypertensive humans.34 Felodipine is a structural analogue of nifedipine and is highly vasoselective.23,35 It seems unlikely that nonspecific vasodilation is the mechanism underlying the subcutaneous vascular responses to upright tilt observed in the present study.

In agreement with the concept of selective autonomic control of the regional circulations,1 forearm subcutaneous vascular resistance has been shown to be modulated by cardiopulmonary and not arterial baroreceptors during upright tilt.6 The substantial decrease in forearm subcutaneous vascular resistance observed during tilt in patients on placebo was not only abolished but reversed after the proximal neural blockade, probably due to the observed augmentation of humoral norepinephrine levels. The local β-adrenoceptor blockade before and after the combination with the proximal neural blockade caused about the same increments in forearm subcutaneous vascular resistance during tilt on placebo. This would suggest that vascular β-adrenoceptors were neurally rather than humorally activated. Confirming previous findings,19 these observations seem to indicate that the tilt-induced subcutaneous vasodilation in such patients is an efferent β-adrenergic reflex effect. The increments in plasma epinephrine levels observed during upright tilt in our patients with CHF do not occur in normal subjects19,20 and may relate to a cotransmitter role for epinephrine in these patients.20

Rather than a direct vasodilator effect, the effect of felodipine on forearm subcutaneous vascular resistance appears to be centrally elicited and transmitted neurogenically to subcutaneous resistance vessels. The drug tended to normalize the subcutaneous vascular

**FIGURE 5.** Effects of local β-adrenoceptor blockade on the tilt-induced relative changes in forearm subcutaneous vascular resistance during the two treatment courses in patients with CHF.

**FIGURE 6.** Mean relative changes in subcutaneous blood flow and forearm subcutaneous vascular resistance caused by upright tilt during combined local β-adrenoceptor and proximal neural blockade after 3 weeks of adjunctive therapy with placebo (P) or felodipine (F) in patients with CHF.
responses to upright tilt (figure 3). It is difficult to explain such directionally opposite changes in forearm subcutaneous vascular resistance by the observation that the drug reduced forearm subcutaneous vascular resistance under supine reference conditions. Furthermore, reference forearm subcutaneous vascular resistance during felodipine therapy was further reduced after the proximal neural blockade. This blockade did not only fail to increase, but reduced forearm subcutaneous vascular resistance in patients in the tilted position (figure 4), despite the augmentation of circulating norepinephrine levels. Such vasodilation may relate to calcium channel–blocking properties of felodipine on the blood vessel wall,\textsuperscript{22, 23} preventing vasoconstrictor rather than vasodilator effects of the elevated humoral levels of catecholamines. Like during the placebo period and in a similar recent study,\textsuperscript{19} the local \(\beta\)-adrenoceptor blockade during the felodipine period caused a substantial vasoconstrictor response to upright tilt (figure 5). This vasoconstriction seems to be modulated by neural vasoconstrictor impulses since it was completely abolished after the addition of proximal neural blockade (figure 6). The results suggest that the attenuated increment in forearm subcutaneous vascular resistance during tilt in patients on felodipine may represent a centrally integrated net response to two efferent pathways, an \(\alpha\)-norepinephrine and a \(\beta\)-epinephrine pathway, in such patients.\textsuperscript{19, 20}

The coordinated cardiovascular response to upright tilt is modulated mainly by cardiopulmonary and arterial baroreflexes and is normally intended to preserve the arterial blood pressure.\textsuperscript{1} The existence of arterial hypotension and unaltered heart rate, together with peripheral vasodilation during upright tilt on placebo, is another example of the profoundly impaired baroreflex cardiovascular control previously reported in patients with CHF.\textsuperscript{19, 20, 36} Selective impairment of the cardiopulmonary baroreflex has been proposed,\textsuperscript{36} but it probably cannot exist without an associated abnormality in the arterial baroreflex in such patients. Afferent activity from cardiopulmonary baroreceptors is known to exert a significant restraint on reflex sympathetic activation induced by arterial baroreceptor hypotension.\textsuperscript{1} Consequently, a decrease in this activity during upright tilt has been reported to augment the arterial baroreflex in man,\textsuperscript{1, 4} while an increase in the same activity during augmentation of cardiac filling\textsuperscript{1} has been shown to reduce the arterial baroreflex sensitivity.\textsuperscript{1, 37, 38}

Depressed baroreceptor afferent activity and degenerative changes in cardiopulmonary\textsuperscript{16, 17} and arterial\textsuperscript{15} baroreceptor afferent endings have been observed in studies of heart failure. After lidocaine blockade of vagus and glossopharyngeal nerves in the human neck,\textsuperscript{39} the normally differentiated sympathetic efferent outflow\textsuperscript{1} has been shown to become uniform in subcutaneous and skeletal muscle vascular beds.\textsuperscript{39} This temporary deafferentation of cardiopulmonary and arterial baroreceptors has also been shown to cause the appearance of abnormal sympathetic reflexes.\textsuperscript{39} The abnormal \(\beta\)-adrenergic reflex vasodilation that has been uniformly demonstrated in skeletal muscle\textsuperscript{20} and subcutaneous tissue\textsuperscript{19} during tilt in subsets of patients similar to those we studied could thus be a manifestation of reduced supraspinal afferent restraint from both baroreceptor sites and may relate to the severity of depression of baroreceptor sensitivity during CHF.

Depressed baroreceptor afferent restraint would explain the neurohumoral excitation\textsuperscript{11–13} but not the attenuated cardiovagal efferent control\textsuperscript{9} reported in patients with CHF. Increased cardiac pressures and dimensions accompanying CHF may activate spinal positive-feedback sympathosympathetic reflexes that have been shown to be sensitive to such stimuli in normal animals.\textsuperscript{40–43} Activation of these reflexes has been demonstrated to reduce both baroreflex sensitivity\textsuperscript{42} and cardiovagal efferent discharge.\textsuperscript{40} Excitation of aortic sympathetic afferents has been achieved by mechanic\textsuperscript{42} or pulsatile\textsuperscript{41} stretch of thoracic aorta, even after ischemic damage of aortic wall.\textsuperscript{41, 43} Studies of the aortic pulsatile pressure and radius relationship in normal animals\textsuperscript{44} and man\textsuperscript{45} have disclosed that the pressure is the dominant variable controlling the radius\textsuperscript{44} and that a reduction in diastolic pressure would lower the corresponding aortic diameter.\textsuperscript{45} Despite the lowered arterial mean and unaltered pulse pressure observed both during tilt in patients on placebo and in those on felodipine in the supine position, the aortic diastolic diameter was almost unchanged and failed to decrease (tables 1 and 2). However, under both of these conditions, the aortic pulsatile stretch increased substantially together with modest, albeit significant, increments in plasma norepinephrine levels.

Felodipine therapy could have affected the mechanical stimulus to arterial baroreceptors. As shown in figure 2, the aortic pulsatile stretch increased during tilt on placebo, stimulating aortic baroreceptors and promoting vasodilation, whereas it decreased during tilt on felodipine, deactivating aortic baroreceptors and promoting vasoconstriction. However, baroreceptor stimulation is known to reflexly reduce sympathetic efferent activity. Studies of blockade of efferent neural impulses in patients with CHF\textsuperscript{19, 20} suggest an increment in efferent neural activity during tilt in such pa-
tients. Although aortic pressure is reported to be a dominant variable controlling aortic radius,44, 45 only changes in aortic pressure and pulse pressure are reported to be stimuli to arterial baroreceptors.1-5, 36, 46, 47 It is therefore possible that the changes in aortic pulsatile stretch observed in the present study relate to positive rather than negative feedback reflexes. The possibility exists that, besides baroreflexes, excitatory reflexes are involved in circulatory homeostasis during the course of CHF.

Depressed sensitivity of cardiopulmonary and arterial baroreceptors in CHF may be related in part to chronic cardiac dilatation14, 46 and augmented afterload.1, 46 During therapy with felodipine, afterload was reduced and left ventricular systolic function was improved, as evidenced by marked and preferential increments in stroke volume and aortic systolic distension, both of which imply a corresponding decrease in left ventricular end-systolic volume. During tilt in patients on felodipine, modest but substantial increments in heart rate and systemic vascular resistance contributed to the maintenance of arterial blood pressure. Such cardiovascular responses to unloading of cardiopulmonary (lowered cardiac filling) and arterial baroreceptors (lowered pulse pressure) indicate normalization of a centrally integrated baroreflex efferent control of peripheral vascular resistance and heart rate.1, 47 This, taken together with the observation that the cardiopulmonary baroreflex modulation of forearm subcutaneous vascular resistance is normalized during felodipine therapy, suggests sensitization of cardiopulmonary and arterial baroreceptors by the drug in patients with CHF. There is increasing evidence suggesting that beneficial effects of digitalis in individuals with heart failure are related to sensitization of baroreceptors.47 Such an effect of felodipine may have clinical implications for the therapeutic use of this agent.

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