Amlodipine, Enalapril, and Dependent Leg Edema in Essential Hypertension

Roberto Pedrinelli, Giulia Dell’Omo, Elio Melillo, Mario Mariani

Abstract—Calcium channel blockers (CCBs) blunt postural skin vasoconstriction, an autoregulatory mechanism that minimizes gravitational increases in capillary pressure and avoids fluid extravasation when standing. To evaluate the dose-response relation between this pharmacological interference and dependent edema, a frequent side effect of CCBs during antihypertensive treatment, skin blood flow (laser Doppler flowmetry) at the dorsum of the foot, both supine and with the limb passively placed 50 cm below the heart level, and leg weight (Archimedes principle) were measured at baseline, during increasing doses of the dihydropyridine amlodipine (5 and 10 mg UID each for 2 weeks), and after drug withdrawal in 10 hypertensive men. Because angiotensin-converting enzyme inhibitors may attenuate ankle swelling by CCBs, those parameters were evaluated according to a similar design during amlodipine (10 mg UID) and enalapril (20 mg UID) combined (n = 10). As a control, the effect of enalapril monotherapy (10 and 20 mg UID for 2 weeks each) was evaluated in a third series of patients (n = 8). Amlodipine (5 mg UID) increased leg weight without modifying postural vasoconstriction (the percent skin blood flow decrease from horizontal to dependent position), which indicates that extravascular fluid shift was independent of postural skin vasoconstriction. At 10 mg UID, however, amlodipine blunted postural vasoconstriction and increased leg weight further, which suggests that skin blood flow autoregulation limited additional fluid transfer. Both parameters normalized after drug withdrawal. Enalapril per se did not affect cutaneous vasomotion or leg weight but reduced the amount of dependent fluid extravasation by the CCB despite a persistent antagonism for postural vasoconstrictor responses. (Hypertension. 2000;35:621-625.)

Key Words: calcium antagonists ■ angiotensin-converting enzyme inhibitors ■ blood flow ■ vasoconstriction ■ hypertension, essential

Precapillary resistance in the skin of the foot rises on standing, thereby limiting the increase in capillary pressure resulting from gravitational increases in transmural pressure.1,2 This autoregulatory vasoconstrictor mechanism is triggered by limb venous congestion and operates both through a locally evoked sympathetic axoaxonic reflex1,3 and local myogenic factors,3 with some minor participation of central mechanisms.2 The postural vasoconstrictor response protects subcutaneous tissue from fluid extravasation during dependency and eventually dependent edema4; its derangement, as in patients with peripheral vascular disease4 and diabetes,5 sets the stage for subcutaneous edema formation.6 We have recently shown impaired postural skin blood flow control in patients with essential hypertension who were treated with calcium channel blockers (CCBs).7 This pharmacological effect may contribute to ankle and/or pretibial edema in the absence of fluid retention,8 a frequent, bothersome, and still not completely understood collateral effect of calcium antagonist drugs.9

To test this hypothesis, we evaluated the relation between changes in postural skin vasomotion and objective measures of ankle swelling during treatment with graded doses of amlodipine, a dihydropyridine CCB.10 On the basis of previous reports of reduced ankle swelling during association therapy with angiotensin-converting enzyme inhibitors (ACEIs),11,12 we evaluated those parameters also during amlodipine treatment combined with enalapril, an ACEI.13 Skin blood flow was measured with the use of laser Doppler flowmetry (LDF), a noninvasive method that registers the sudden changes evoked by posture1,5,14 without entailing local vasomotor reflexes. Fluid extravasation was indirectly assessed by measuring changes in leg weight by use of the Archimedes principle to measure water displacement induced by immersion of the leg.

Methods

Patients

The study was performed in 28 patients (age range 33 to 70 years) with uncomplicated stage I to II mild essential hypertension diagnosed by exclusion of secondary causes through history, physical examination, routine blood chemistry, and laboratory examinations. Only men were studied to avoid possible influences of menstrual cycles on systemic fluid status. All subjects had ankle/brachial systolic blood pressure (SBP) ratios of >1.0; none complained or
showed evidence of venous disease. Patients were either never treated or had not received treatment for 1 month at the moment of the first baseline determination.

**Experimental Protocol**

The studies were performed between 2 and 4 PM and ≥2 hours after the last food, drink, or smoking. Drugs were taken at approximately 8 AM, and measurements were obtained 6 to 8 hours from the last dosing. Patients were at ease with the medical staff and lay supine for 30 minutes in a quiet, climatized room (22° to 24°C) at constant barometric pressure (range 756 to 768 mm Hg) and humidity (range 35% to 41%).

The general structure of the study consisted of measurement of LDF, leg weight, and blood pressure (BP) (1) at baseline, (2) after 30 minutes in a quiet, climatized room (22° to 24°C) at constant dosing. Patients were at ease with the medical staff and lay supine for 8 AM, and measurements were obtained 6 to 8 hours from the last food, drink, or smoking. Drugs were taken at approximately 2 hours after the maneuver dripped into a container set on a kitchen scale, thus allowing accurate (within 5 g) and reproducible (average variation coefficient 0.8%, n = 5 determinations in 5 normal subjects) measurements.

**Series 1 (n=10, age 54±6 years)**

To characterize the dose-response profile of microvascular and fluid parameters to amlopidine, the drug was started at 5 mg UID for 2 weeks, increasing the dosage to 10 mg UID during the final 2 weeks.

**Series 2 (n=10, age 58±9 years)**

The interaction between calcium channel blockade and angiotensin-converting enzyme inhibition was assessed by adding amlopidine (10 mg UID×2 weeks) in patients who received enalapril (20 mg UID) for the preceding 2 weeks.

**Series 3 (n=8, age 58±7 years)**

To evaluate the pattern of response to enalapril at different doses, a third group of patients was given 10 mg UID enalapril during the first 2 weeks and 20 mg UID enalapril during the final 2 weeks.

**Experimental Methods**

**Laser Doppler Flowmetry**

Skin blood flow was recorded with the use of a laser Doppler flowmeter (Periflux 4001 Master, Perimed Ltd). The device contains a solid-state, low-power diode laser (1 mW at the probe tip, wavelength 780 nm) that delivers a laser light to a cutaneous surface of ~1 mm² at a depth of ~1 mm through flexible, graded-index, fiberoptic light guides. The laser light strikes moving red blood cells and is reflected with a shift in frequency, whereas nonmoving structures cause no shift in frequency. The reflected light is guided from the tissue surface through a second fiberoptic light guide, mixed, and analyzed in real-time by an analogue processor that provides a continuous output of the instantaneous mean Doppler frequency in the photocurrent identified by a square-law detector; the digitized signal was fed into a computer for on-line and off-line analyses. Before each study, the instrument was made null for a condition of no flow by placing the laser probe in the calibration clip containing no mobile structures and calibrated into a solid-state, low-power diode laser (1 mW at the probe tip, wavelength 780 nm) that delivers a laser light to a cutaneous surface of ~1 mm² at a depth of ~1 mm through flexible, graded-index, fiberoptic light guides. The laser light strikes moving red blood cells and is reflected with a shift in frequency, whereas nonmoving structures cause no shift in frequency. The reflected light is guided from the tissue surface through a second fiberoptic light guide, mixed, and analyzed in real-time by an analogue processor that provides a continuous output of the instantaneous mean Doppler frequency in the photocurrent identified by a square-law detector; the digitized signal was fed into a computer for on-line and off-line analyses. Before each study, the instrument was made null for a condition of no flow by placing the laser probe in the calibration clip containing no mobile structures and calibrated into a

Biological zero (ie, the laser Doppler flux recorded under no-flow conditions) was not subtracted because the precise nature of this measurement is still undetermined.15,16 Time-constant and sampling frequency were set at 0.03 seconds and 16 Hz, respectively. Double-sided adhesive disks were attached to the probes, which then were applied to the skin of the dorsal surface (first intermetatarsal space) of the right foot and left foot, an anatomic region characterized by predominance of precapillary arterioles7 under control of the intrinsic myogenic tone.3,18 Therefore LDF at this site reflects mainly nutritional capillary blood flow,18 which is to a large extent independent of sympathetic stimuli.7,18

Results (expressed in perfusion units, PU, were 1 PU equals 10 mV measured on the analogue output) were computer-derived, smoothed averages (Perisoft, Perimed Ltd) of skin blood flow recordings during the 2 minutes preceding foot lowering (leg dangling 50 cm below the heart level) and at the 9th and 10th minutes of foot dependency, when the parameter was invariably constant in all patients. Data measured at the heart (H) level and during dependency (D) were used to calculate percent postural changes [(H-D)/H×100] as a measure of postural vasoconstriction. Intraindividual variability of the method as performed in our laboratory has been reported.7

**Leg Weight**

Leg weight was measured immediately after the LDF session with patients sitting comfortably on a chair. The right and left limbs were consecutively immersed up to the inner tibial tuberosity in a Plexiglas cube that contained lukewarm water (36° to 37°C) to avoid sudden vasoconstrictor responses. The entire water volume displaced by the maneuver dripped into a container set on a kitchen scale, thus allowing accurate (within 5 g) and reproducible (average variation coefficient 0.8%, n = 5 determinations in 5 normal subjects) measurements.

**TABLE 1. Laser Doppler Flowmetry at the Dorsum of the Foot (Heart Level and During Dependency), Leg Weight, and Blood Pressure During Amlodipine**

<table>
<thead>
<tr>
<th>Evaluation Variables</th>
<th>Amlodipine, 5 mg UID</th>
<th>Amlodipine, 10 mg UID</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDF&lt;sub&gt;heart&lt;/sub&gt;, PU</td>
<td>5.8 (2.0)</td>
<td>8.8 (5.3)*</td>
<td>10.7 (8.5)**</td>
</tr>
<tr>
<td>LDF&lt;sub&gt;dependency&lt;/sub&gt;, PU</td>
<td>2.9 (1.8)</td>
<td>4.2 (4.4)</td>
<td>9.4 (12)**</td>
</tr>
<tr>
<td>Leg weight, g</td>
<td>3232±319</td>
<td>3319±319†</td>
<td>3368±309†</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>158±18</td>
<td>146±9‡</td>
<td>142±13‡</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>98±14</td>
<td>89±10‡</td>
<td>84±11‡</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>119±15</td>
<td>108±9‡</td>
<td>103±11‡</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or mean±SD. *P=0.05, †P=0.02, ‡P=0.01 vs baseline.

**TABLE 2. Laser Doppler Flowmetry at the Dorsum of the Foot (Heart Level and During Dependency), Leg Weight, and Blood Pressure During Enalapril**

<table>
<thead>
<tr>
<th>Evaluation Variables</th>
<th>Enalapril, 10 mg UID</th>
<th>Enalapril, 20 mg UID</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDF&lt;sub&gt;heart&lt;/sub&gt;, PU</td>
<td>7.2 (2.3)</td>
<td>6.6 (3.1)</td>
<td>8.4 (2.8)</td>
</tr>
<tr>
<td>LDF&lt;sub&gt;dependency&lt;/sub&gt;, PU</td>
<td>3.2 (1.9)</td>
<td>2.6 (1.1)</td>
<td>4.0 (1.4)</td>
</tr>
<tr>
<td>Leg weight, g</td>
<td>3183±252</td>
<td>3200±245</td>
<td>3174±234§</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>147±13</td>
<td>137±15*</td>
<td>139±14*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>93±9</td>
<td>82±8§</td>
<td>86±9</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>111±10</td>
<td>100±9§</td>
<td>103±10*</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or mean±SD. *P=0.05, †P=0.02, ‡P=0.01 vs baseline.
Results

Baseline parameters were comparable in the patients allocated to the 3 different series (Tables 1, 2, and 3).

Laser Doppler Flowmetry

Resting and dependent skin flow increased dose dependently during amlodipine and recovered after drug withdrawal (Table 1). Postural vasoconstriction was blunted (P<0.006 versus baseline) only at the 10-mg UID dose because of a lesser decrease in dependent flow (Table 1 and Figure 1, left).

Microvascular parameters did not change during enalapril (Tables 2 and 3). Postural vasoconstriction was significantly blunted (P=0.03 versus baseline) by 10 mg UID amlodipine, even in enalapril-pretreated patients (Table 3 and Figure 2, left). The amount of inhibition induced by the CCB given alone or in combination did not differ (compare Figure 1 with Figure 2, left).

Leg Weight

No patient developed clinical evidence of ankle and/or pretibial pitting edema. Amlodipine increased leg weight by a median of 80 (68) g (P=0.006 versus baseline) at 5 mg and by an additional 68 g (65, P=0.059 versus 5 mg) at 10 mg, a cumulative increment of 136 g (range 40 to 230, P=0.006 versus baseline). Weight returned toward normal after drug withdrawal (Table 1 and Figure 1, right).

Leg weight did not change during enalapril (Tables 2 and 3) and increased when 10 mg UID amlodipine was added in enalapril-pretreated patients (Table 3 and Figure 2, right).

Weight gains during amlodipine (10 mg UID) with enalapril (20 mg UID) treatment were comparable to those observed during amlodipine monotherapy at one half that dosage [60 (90) versus 80 (68) g, respectively].

Blood Pressure

Amlodipine and enalapril decreased SBP, DBP, or both (Tables 1 and 2) without a dose-dependent relation. When the 2 drugs were combined (Table 3), BP dropped additively (mean percent MBP decrement: 10 mg UID amlodipine and 20 mg UID enalapril combined, 18%; 10 mg UID amlodipine, 13%; and 20 mg UID enalapril, 7%).

Correlations

The correlation between the intraindividual increments in leg weight and the decrements in postural vasoconstriction was not statistically significant, either in the overall group (r=−0.31, P=0.17, n=20) or in the subgroups of patients treated with amlodipine per se (r=−0.30, P=0.36, n=10) or combined with enalapril (r=−0.12, P=0.7, n=10) (Figure 3).

Discussion

The aim of this clinical study was to evaluate the relation between skin blood flow autoregulatory vasoconstriction and dependent fluid extravasation during calcium channel blockade. The importance of this research stems from the present knowledge on the physiological role played by the local
vasoconstrictor skin reflexes in humans.\textsuperscript{1,2} In fact, precapillary vasoconstriction caused by local myogenic factors and a locally evoked sympathetic axoaxonic reflex\textsuperscript{1–3} modulates gravitational increments in capillary pressure and brakes fluid filtration by raising plasma oncotic pressure as a consequence of slowed microvascular blood flow.\textsuperscript{19–22} Our data confirm previous results from our laboratory\textsuperscript{7} and other\textsuperscript{23} laboratories that show an antagonism of postural cutaneous vasoconstriction by CCBs, apparently not a specific property of dihydropyridines because verapamil, a chemically unrelated drug, behaved similarly.\textsuperscript{7} Influences from nonspecific vasorelaxation or functional antagonism against physiological vasoconstrictor mechanisms also could be excluded because \(\alpha\)-adrenoceptor blockers and angiotensin AT-1 receptor blockers such as doxazosin and losartan, respectively, were ineffective on cutaneous microcirculation.\textsuperscript{7} It is more probable that blunted postural vasoconstriction by CCBs reflected modulation of calcium fluxes\textsuperscript{24} maintaining myogenic tone, an extracellular calcium-dependent process\textsuperscript{25} involved in skin blood flow autoregulation.\textsuperscript{3} Our findings also show dose-dependent limb weight gains during administration ofamlodipine, an interesting finding that indicates that dependent edema should not be seen as an occasional adverse event of CCBs, either dihydropyridines\textsuperscript{6} or no dihydropyridine (eg, see References 26 and 27), but rather the extreme phenotype of a highly consistent pharmacological effect. In the context of our specific aims, though, the main outcome of the study was to show coexistence of dependent fluid extravasation with preserved postural control of skin blood flow by 5 mg UID amlodipine. Therefore net extravascular fluid shifts may occur independent from any interference with postural reflex skin vasoconstriction, in line with the knowledge about the multifactorial control of capillary fluid filtration and Starling’s equilibrium.\textsuperscript{28} However, preserved autoregulation during the 5-mg amlodipine dosing probably prevented additional interstitial edema accumulation in the dependent limb because limb weight showed further gains when postural vasomotion was impaired by a higher dose of the drug. This plausible conclusion, supported by a consistent body of evidence (see above), is somewhat tentative because the intraindividual correlation between gain in leg weight and attenuation of postural vasoconstrictor responses was not statistically significant. However, a correlation would not establish cause-effect relations nor could it exclude the influence of third unknown variables. Therefore additional mechanistic studies are needed to delineate more exactly the role of postural vasomotion and dependent edema during CCBs.

In agreement with previous observations obtained with drugs belonging to similar pharmacological classes,\textsuperscript{11} enalapril restrained fluid extravasation by amlodipine in that weight increments during combined treatment at 10 mg UID were similar to those induced by CCB monotherapy at one half that dosage. This clinically favorable property compounds the additive antihypertensive effect of association therapy with CCBs and ACEIs, documented again and again since the first descriptions.\textsuperscript{29} Besides inhibiting angiotensin II production, ACEIs may increase bradykinin levels, enhance the release of prostaglandins, and depress \(\alpha\)-adrenergic responsiveness.\textsuperscript{30} None of those biological systems, however, appear to maintain or assist the postural increase in skin precapillary resistance associated with lowering one extremity below heart level, because enalapril did not alter the postural reflex control of skin vascular resistance nor did it interfere with the antagonistic effect of amlodipine. As a consequence, the attenuation of dependent fluid extravasation by the ACEI probably occurred by different biological mechanisms. Perhaps a complex interplay might take place at the microcirculatory level between more effective inhibition of precapillary resistance vessels by the CCB\textsuperscript{31} and preferen-
tial venodilatation by the ACEI,\textsuperscript{32} with a resulting limitation of the rise in capillary pressure. We have, however, no data in favor of or against this possibility.

In conclusion, amlodipine, a dihydropyridine CCB, increased intravascular fluid filtration to the extravascular compartment through mechanisms independent of interference with postural reflex skin vasoconstruction; however, effective skin blood flow autoregulation may have limited excessive fluid filtration. Pretreatment with enalapril, an ACEI, attenuated dependent fluid extravasation by amlodipine without modifying its antagonism for postural vasoconstruction.

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