Omapatrilat Reduces Pulse Pressure and Proximal Aortic Stiffness in Patients With Systolic Hypertension

Results of the Conduit Hemodynamics of Omapatrilat International Research Study

Gary F. Mitchell, MD; Joseph L. Izzo, Jr, MD; Yves Lacourcière, MD; Jean-Pascal Ouellet, MD; Joel Neutel, MD; Chunlin Qian, PhD; Linda J. Kerwin, MS; Alan J. Block, PhD; Marc A. Pfeffer, MD, PhD

Background—Increased pulse pressure, an indicator of conduit vessel stiffness, is a strong independent predictor of cardiovascular events in hypertensive cohorts, which suggests that reduction of conduit vessel stiffness may be desirable in hypertension.

Methods and Results—We assessed changes in pulse pressure and conduit vessel stiffness in a 12-week double-blind, randomized clinical trial that compared monotherapy with the ACE inhibitor enalapril 40 mg daily (n=87) versus the vasopeptidase inhibitor omapatrilat 80 mg daily (n=80) in patients with systolic hypertension. Patients were withdrawn from antihypertensive medications 1 to 2 weeks before enrollment, and systolic pressure was confirmed to be ≥160 mm Hg. With the use of calibrated tonometry and pulsed Doppler, pulsatile hemodynamics were assessed before randomization and at 12 weeks. Characteristic impedance ($Z_c$), a direct measure of the stiffness of the central aorta, was calculated from the ratio of changes in carotid pressure and aortic flow in early systole. Omapatrilat compared with enalapril produced greater reductions in peripheral ($-8.2\pm12.2$ versus $-4.0\pm12.2$ mm Hg, $P<0.05$) and central ($-10.2\pm16.2$ versus $-3.2\pm16.9$ mm Hg, $P<0.01$) pulse pressures and $Z_c$ ($237\pm83$ to $208\pm70$ versus $225\pm87$ to $231\pm94$ dyne · s/cm$^2$, $P<0.001$); the latter remained significant ($P<0.05$) after adjusting for change in mean pressure.

Conclusions—Greater reductions in pulse pressure and $Z_c$ in hypertensive subjects treated with omapatrilat compared with enalapril suggest that aortic stiffness is maintained by specific, partially reversible mechanisms and underscore a potential role for pharmacological modulation of natriuretic peptides in the treatment of hypertension. (Circulation. 2002;105:2955-2961.)

Key Words: hypertension ■ hemodynamics ■ aorta ■ natriuretic peptides

Increased pulse pressure, an indirect indicator of increased conduit vessel stiffness, recently has emerged as a strong independent predictor of cardiovascular events in the general population$^1$ and in patients with hypertension.$^{2,3}$ Conduit vessel stiffening increases the amplitude of the pressure wave produced by a given flow wave in the central aorta and increases the propagation velocity of pressure waves, which leads to earlier return of reflected pressure waves to the central aorta, where they additionally augment central systolic and pulse pressure and left ventricular load. Such increased pulsatile load may promote ventricular and vascular hypertrophy and fibrosis,$^{4,5}$ endothelial dysfunction,$^6$ and atherogenesis$^7$ and may explain the observed association between pulse pressure and clinical events.

The increasing prevalence of systolic hypertension and the excess risk associated with increased pulse pressure have stimulated interest in defining interventions that specifically reduce conduit vessel stiffness. ACE inhibitors may reduce stiffness of conduit vessels by opposing vasoconstrictive, hypertrophic, and profibrotic effects of angiotensin II on the vessel wall.$^8$ The vasopeptidase inhibitor omapatrilat is a single molecule that inhibits both ACE and neutral endopep-

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From Cardiovascular Engineering, Inc (G.F.M.), Holliston, Mass; State University of New York at Buffalo (J.L.I.), Buffalo, NY; Centre hospitalier de l’Université Laval (Y.L.), Ste Foy, Quebec; Q&T Research, Inc (J.-P.O.), Sherbrooke, Quebec, Canada; Orange County Research Center (J.N.), Orange, Calif; Bristol-Myers Squibb Pharmaceutical Research Institute (C.Q., L.J.K., A.J.B.), Princeton, NJ; and Brigham and Women’s Hospital (M.A.P.), Boston, Mass.

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Correspondence to Gary F. Mitchell, MD, Cardiovascular Engineering, Inc, 327 Fiske St, Holliston, MA 01746. E-mail: GaryFMitchell@mindspring.com

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tidase (NEP), an enzyme that inactivates several vasodilatory peptides, including the natriuretic peptides (NPs), which are thought to play a role in the body’s defense against hypertension. Thus, omapatrilat reduces levels of angiotensin II and increases levels of vasodilatory peptides, including NPs, bradykinin, and adrenomedullin. Prior studies in experimental models suggest that the NPs may have favorable effects on conduit vessels. Therefore, we designed this trial to compare changes in pulse pressure and central pulsatile hemodynamics after ACE inhibition with enalapril or vasopeptidase inhibition (VPI) with omapatrilat in patients with systolic hypertension.

**Methods**

**Study Subjects**

Male or female subjects age ≥18 years were eligible for initial enrollment if they were in sinus rhythm and had systolic or mixed systolic-diastolic essential hypertension, defined as a seated systolic blood pressure ≥160 mm Hg if newly diagnosed or ≥140 mm Hg if presently treated and diastolic blood pressure ≤110 mm Hg. Patients with a history of transient ischemic attacks within the prior 12 months or myocardial infarction or angina within the prior 6 months were ineligible. All patients with heart failure, documented ejection fraction <45%, valvular heart disease, or clinically significant peripheral vascular disease were excluded. Additional exclusion criteria included renal or renovascular disease, uncontrolled diabetes (glucose >200 mg/dL fasting or >220 mg/dL nonfasting), autoimmune disease, multiple drug allergies, or bronchospastic disease requiring ongoing medications. Laboratory exclusion criteria included a hemoglobin <9 g/dL, platelet count <80,000/μL, white cell count <3000/μL, neutrophil count <1500/μL, serum potassium <3.5 or >5.2 mmol/L, alanine aminotransferase or aspartate aminotransferase >3 times the upper limits of normal, or serum creatinine >2.5 mg/dL. Failure to obtain a technically satisfactory baseline study, as determined by the core laboratory, was an exclusion criterion. If an initial baseline study had potentially remediable technical limitations, a repeat study was allowed within 2 to 9 days. An institutional review board at each clinical center approved the study protocol, and each patient gave written informed consent before enrollment.

**Treatment Protocol**

After withdrawal of all antihypertensive medications, patients entered a single-blind placebo lead-in period of 1 to 2 weeks, during which the seated systolic blood pressure was confirmed to be ≥160 mm Hg and <200 mm Hg and the diastolic pressure ≤110 mm Hg. This was followed by a double-blind active treatment period of 12 weeks. Baseline hemodynamic studies were performed at the end of the placebo lead-in period between 6:00 AM and 10:00 AM, with the patient in a fasting state before taking morning medications and off all antihypertensive medications for at least 1 week. Patients were randomized within 2 to 9 days after an approved baseline study. The goal of this mechanistic study was to compare the relatively short-term effects of maximal doses of the chosen treatments as monotherapy. Therefore, we used a forced-titration approach that ensured safe yet rapid and parallel exposure to maximal doses of study medication. Treatment was initiated with either 10 mg omapatrilat or 10 mg enalapril and was titrated at 2 and 4 weeks to doses of 40 and then 80 mg omapatrilat or 20 and then 40 mg enalapril. Patients who failed to tolerate at least 40 mg omapatrilat or 20 mg enalapril were excluded from the study. No concomitant antihypertensive medications were permitted during the study. A trough hemodynamic study was performed at the end of the active treatment period, 24 hours after the last prior dose of study medication, under identical conditions as the baseline study.

**Hemodynamic Data Acquisition**

Subjects were studied in the supine position after ~10 minutes of rest. With the use of a computer-controlled device, auscultatory blood pressure was obtained at 2-minute intervals with a goal of obtaining 3 sequential readings that agreed to within 5 mm Hg for systolic and diastolic pressures. Arterial tonometry with ECG was obtained from the brachial, radial, femoral, and carotid arteries with a custom transducer. Next, echocardiographic images of the left ventricular outflow tract were obtained from a parasternal long-axis view. This was followed by duplicate acquisitions of simultaneous tonometry of the carotid artery and pulsed Doppler of the left ventricular outflow tract from an apical 5-chamber view. Finally, body surface measurements from suprasternal notch to radial, femoral, and carotid recording sites were obtained. All data were digitized during the primary acquisition (ECG and tonometry pressures at 1000 Hz, audio at 12 kHz, and video at 30 frames/s), transferred to CD-ROM, and shipped to the core laboratory at Cardiovascular Engineering, Inc, for analysis.

**Data Analysis**

All studies were analyzed in blinded fashion. Tonometry waveforms were signal-averaged with the ECG as fiducial point. Blood pressures were over-read during analysis. Average systolic and diastolic cuff pressures were used to calibrate peak and trough of the signal-averaged brachial pressure waveform. Diastolic and integrated mean brachial pressures were then used to calibrate carotid, radial, and femoral pressure tracings. Pulse wave velocities (PWVs) were calculated as shown in Figure 1. Characteristic impedance (Zc), reflected wave transit time, and augmentation index were calculated as shown in Figure 2. Proximal aortic compliance per unit length was calculated as previously described. As previously reported, reproducibility of measures of central aortic stiffness using our protocol in a multicenter setting is high, with intraclass correlation coefficients for repeated measures of Zc or proximal aortic compliance of 0.93 to 0.95.

**Statistical Analysis**

Baseline characteristics were tabulated and compared by means of a χ² statistic for dichotomous variables and ANOVA for continuous variables.
variables. Significance levels of within-group comparisons of the change from baseline in continuous variables were assessed by a paired t test. Significance levels of between group comparisons of the change from baseline in continuous variables were assessed by a general linear model that adjusted for baseline value. Pressure independence of changes in stiffness parameters was assessed by including baseline mean pressure and change in mean pressure in the model. Values are presented as mean±SD except as noted in the Figures. A 2-sided P value of <0.05 was considered significant.

Results

Of 335 enrolled subjects, 213 completed the single-blind lead-in period, met entry criteria, and were randomized to active treatment. Of these, 185 subjects completed the active treatment period and 167 had technically adequate paired assessments of all hemodynamic parameters. Baseline characteristics of the treatment groups were similar and consistent with a population having moderate systolic hypertension (Tables 1 through 3). There were no differences between treatment groups in any baseline hemodynamic parameters (Tables 2 and 3).

As anticipated, both therapies reduced systolic, diastolic, and mean arterial pressure (MAP). However, omapatrilat produced greater reductions in all trough blood pressure parameters, including peripheral and central pulse pressure (Table 2). Neither treatment had an effect on heart rate or peak aortic flow, whereas peripheral resistance was reduced more by omapatrilat. Omapatrilat markedly reduced the amplitude of the forward pressure wave by reducing Zc, in the setting of unchanged peak flow (Tables 2 and 3, Figure 3). There were trends toward greater reductions in carotid-radial and carotid-femoral PWV with omapatrilat (Table 3).

The agents comparably reduced augmentation index (Table 3). Reduced augmentation with omapatrilat was associated with increased reflected wave transit time, which indicates later return of the reflected wave, and reduced temporal overlap between forward and reflected wave (Table 3). In contrast, reduced augmentation with enalapril was associated with shortening of the systolic ejection period, which was not seen with omapatrilat (Table 3).

Because many measures of conduit vessel stiffness are pressure dependent, the change in Zc was adjusted for baseline MAP and change in MAP. The reduction in Zc with omapatrilat remained significant (P<0.05). In contrast, the trends toward differential changes in PWVs, which are affected by a combination of central and peripheral conduit properties, were not significant once change in MAP was included in the model. Because assessment of conduit properties at comparable MAP is preferred to statistical adjustment, we divided patients according to quintiles of change in MAP defined for the entire cohort and plotted change in Zc versus change in MAP for each treatment group (Figure 4). With the use of this approach, changes in Zc may be compared at comparable levels of change in MAP; however, group sizes (Figure 4) are not identical within each treatment arm because omapatrilat was more effective at reducing MAP. This plot demonstrates a greater reduction in Zc by omapatrilat than by enalapril at each level of MAP reduction. These analyses demonstrate that 12 weeks of VPI, compared with ACE inhibition alone, had a differential effect on the pressure-stiffness relationship of the proximal aorta, which resulted in a greater reduction in aortic stiffness at comparable levels of change in MAP.

Given the recognized importance of pulse pressure as an emerging cardiovascular risk factor, stepwise multivariable regression analysis was performed to assess relations between

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enalapril</th>
<th>Omapatrilat</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>87</td>
<td>80</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±10</td>
<td>61±9</td>
<td>0.801</td>
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<tr>
<td>Height, cm</td>
<td>169±10</td>
<td>169±9</td>
<td>0.773</td>
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<tr>
<td>Weight, kg</td>
<td>87±18</td>
<td>83±17</td>
<td>0.132</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30±5</td>
<td>29±6</td>
<td>0.206</td>
</tr>
<tr>
<td>Male, %</td>
<td>64</td>
<td>61</td>
<td>0.677</td>
</tr>
<tr>
<td>History of Coronary disease, %</td>
<td>3</td>
<td>5</td>
<td>0.617</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>3</td>
<td>13</td>
<td>0.066</td>
</tr>
<tr>
<td>Active smokers, %</td>
<td>12</td>
<td>13</td>
<td>0.841</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering agent, %</td>
<td>26</td>
<td>24</td>
<td>0.689</td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>21</td>
<td>23</td>
<td>0.776</td>
</tr>
<tr>
<td>Estrogen, % of women</td>
<td>39</td>
<td>39</td>
<td>1.000</td>
</tr>
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</table>
changes in peripheral pulse pressure and hemodynamic load. Candidate variables were $Z_c$, peak flow, MAP, $t_i$, carotid-femoral PWV, carotid-radial PWV, and $P_b/P_f$. Significant correlates (all $P<0.001$) with standardized regression coefficients ($\beta$) were $Z_c$ (0.745), peak flow (0.325), MAP (0.306), and $P_b/P_f$ (0.282). Thus, changes in peripheral pulse pressure were strongly related to changes in $Z_c$ even after adjusting for changes in MAP and wave reflection.

The evaluation of safety included all 213 treated subjects who received at least 1 dose of double-blind study medication. The number of subjects who experienced treatment-emergent adverse events was similar between groups: 76 (73.1%) subjects in the omapatrilat group and 75 (68.8%) subjects in the enalapril group. Twelve subjects treated with omapatrilat and 6 treated with enalapril discontinued because of adverse events. Angioedema or head and neck edema occurred in 3 subjects treated with omapatrilat and 2 subjects treated with enalapril. Baseline hemodynamics in these 5 subjects did not differ from those of the remaining subjects. Of the 3 omapatrilat-treated subjects who experienced these events, 1 had head and neck edema during the placebo lead-in and experienced the event again on day 1 with omapatrilat. No subject in either group was hospitalized for these events; 1 subject in each group discontinued the study after the occurrence of angioedema.

### TABLE 2. Hemodynamic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>Omapatril</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 12</td>
<td>Baseline 12</td>
<td></td>
</tr>
<tr>
<td>Brachial pressures, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>163±15 155±20†</td>
<td>163±15 147±20†</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>85±10 81±10†</td>
<td>84±11 76±11†</td>
<td>0.004</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>78±16 74±20†</td>
<td>79±17 71±18†</td>
<td>0.028</td>
</tr>
<tr>
<td>Mean pressure</td>
<td>117±10 111±12†</td>
<td>117±10 105±13†</td>
<td>0.001</td>
</tr>
<tr>
<td>Central hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>164±18 156±24†</td>
<td>165±19 147±24†</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>79±19 75±23</td>
<td>81±22 71±22†</td>
<td>0.010</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>63±8 63±8</td>
<td>64±9 64±9</td>
<td>0.879</td>
</tr>
<tr>
<td>Mean flow, mL/s</td>
<td>76±17 73±16†</td>
<td>75±19 73±16</td>
<td>0.530</td>
</tr>
<tr>
<td>Peak flow, mL/s</td>
<td>318±73 314±70</td>
<td>311±71 312±68</td>
<td>0.655</td>
</tr>
<tr>
<td>Peripheral resistance, DSC</td>
<td>2172±508 2122±462</td>
<td>2208±567 1986±449†</td>
<td>0.004</td>
</tr>
<tr>
<td>Central stiffness parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First impedance modulus, DSC</td>
<td>354±139 352±163</td>
<td>374±149 323±119†</td>
<td>0.004</td>
</tr>
<tr>
<td>Characteristic impedance, DSC</td>
<td>225±87 231±94</td>
<td>237±83 208±70†</td>
<td>0.001</td>
</tr>
<tr>
<td>Proximal aortic compliance, CD</td>
<td>0.45±0.24 0.49±0.28</td>
<td>0.40±0.19 0.53±0.26†</td>
<td>0.021</td>
</tr>
</tbody>
</table>

DSC indicates dyne cm⁻²; CD, 10⁻¹ cm²/dyne.

* $P$ for difference between therapies in change from baseline, adjusted for baseline value.
† $P<0.05$ for change from baseline within group.

### TABLE 3. PWV and Waveform Morphology

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>Omapatril</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 12</td>
<td>Baseline 12</td>
<td></td>
</tr>
<tr>
<td>Carotid-radial PWV, m/s</td>
<td>10.8±1.8 10.6±1.8</td>
<td>10.8±1.7 10.1±1.4†</td>
<td>0.062</td>
</tr>
<tr>
<td>Carotid-femoral PWV, m/s</td>
<td>12.8±4.0 11.9±3.7†</td>
<td>13.0±4.1 11.4±3.1†</td>
<td>0.076</td>
</tr>
<tr>
<td>Reflected wave arrival time, $t_i$, ms</td>
<td>108±26 108±25</td>
<td>105±23 116±36†</td>
<td>0.024</td>
</tr>
<tr>
<td>Systolic ejection period, ms</td>
<td>325±25 319±27†</td>
<td>323±26 320±26</td>
<td>0.193</td>
</tr>
<tr>
<td>Pressure at $t_i$, mm Hg</td>
<td>144±14 139±17†</td>
<td>145±14 132±20†</td>
<td>0.002</td>
</tr>
<tr>
<td>End-systolic pressure, mm Hg</td>
<td>127±11 120±14†</td>
<td>127±13 114±16†</td>
<td>0.001</td>
</tr>
<tr>
<td>Augmentation index, %</td>
<td>25±11 21±10†</td>
<td>24±10 19±13†</td>
<td>0.256</td>
</tr>
<tr>
<td>Forward wave, $P_f$, mm Hg</td>
<td>59±14 58±17</td>
<td>61±16 54±16†</td>
<td>0.002</td>
</tr>
<tr>
<td>Reflected wave, $P_b$, mm Hg</td>
<td>27±6 27±8</td>
<td>28±7 25±7†</td>
<td>0.046</td>
</tr>
<tr>
<td>$P_b/P_f$ amplitude ratio, %</td>
<td>48±8 46±8</td>
<td>47±7 47±7</td>
<td>0.395</td>
</tr>
<tr>
<td>$P_b$ temporal overlap, %</td>
<td>67±9 66±8</td>
<td>67±8 64±12†</td>
<td>0.044</td>
</tr>
</tbody>
</table>

* $P$ for difference between therapies in change from baseline, adjusted for baseline value.
† $P<0.05$ for change from baseline within group.
This study compared the effects of VPI with omapatrilat and ACE inhibition with enalapril and demonstrated enhanced reduction of central and peripheral pulse pressure with omapatrilat. The hemodynamic mechanism of this enhanced effect on pulse pressure was a reduction in Zc, a direct measure of proximal aortic stiffness, resulting in a smaller forward pressure wave for a given central aortic flow wave. The change in central aortic stiffness was not attributable to the observed differences in mean blood pressure lowering between groups, because differences in Zc remained significant after adjusting for baseline MAP and MAP change during therapy. The reduction in Zc was accompanied by consistent changes in other measures of pulsatile load, including reduced first modulus of impedance, increased proximal aortic compliance, reduced carotid-radial and carotid-femoral PWV, and delayed timing of wave reflection. It is important to note that the effects of omapatrilat on Zc were additive to those achieved by hemodynamically equipotent ACE inhibition alone, which suggests an important role for the NEP-inhibiting effects of this compound in mediating the observed differential change in central aortic stiffness.

VPIs, through inhibition of NEP, increase levels of NPs, which have a potentially favorable role in the treatment of hypertension.9 NPs reduce responsiveness of conduits to vasoconstrictors19 and inhibit hypertrophy20 and hyperplasia21 of vascular smooth muscle cells in vitro. Long-term infusion of NP in spontaneously hypertensive rats increases active and passive carotid compliance and reduces aortic medial thickness in vivo.11 The effect of NPs on conduit vessel tone equals or exceeds their effect on resistance vessels.22 Thus, the conduit vessel wall relaxes as mean pressure falls and vessel diameter remains unchanged or even increases. Because baroreceptors are responsive to changes in vessel wall strain, which remains unchanged, baroreflex-mediated increases in sympathetic tone and heart rate are attenuated or reversed.23–25

Balanced effects of NPs on conduit and resistance vessels have important implications for central pulsatile hemodynamics. Predominant resistance vessel dilators lower MAP and passively (or actively, through sympathetic activation) reduce aortic diameter. As a result, Zc, which is strongly inversely proportional to internal diameter, and pulse pressure may increase even as distending pressure and aortic wall stiffness fall and pulsatile load may rise even as steady-flow load is reduced.18 These unfavorable hemodynamic changes are unlikely with vasodilators that have a balanced effect on conduit and resistance vessel properties. We hypothesized that the foregoing favorable effects of NPs on conduit vessel structure and function would reduce Zc and increase proximal aortic compliance, resulting in a proportionate reduction in the forward pressure wave generated by a given flow wave. An accompanying reduction in PWV in the proximal aorta would improve timing of the reflected wave and reduce central pressure augmentation and late systolic load on the left ventricle. In this multicenter double-blind trial comparing 12 weeks of monotherapy with either omapatrilat or enalapril, we have demonstrated each of these hypothesized changes in central conduit vessel function with omapatrilat.

Increased pulse pressure, an indirect measure of conduit vessel stiffness, has been shown to predict adverse cardiovascular events in patients with hypertension2–5 and in various community-based cohorts.1,26,27 More recently, PWV has been shown to predict adverse events in patients with hypertension28 and in elderly patients.29 Contrary to the popular belief that vascular stiffening is an irreversible age-related process, we have shown that pulse pressure and proximal aortic stiffness are modifiable in hypertension over the course of a fairly brief (12-week) treatment period. The reduction in conduit stiffness may represent structural remodeling or improved modulation of conduit vessel stiffness, either through centrally mediated withdrawal of sympathetic nervous activity23–25 or through improved endothelial function, and may have important implications for clinical events, as was recently demonstrated in a cohort of patients with end-stage renal disease.30 Conduit vessels throughout the arterial system contain a substantial muscular layer, which can modify arterial properties to match vascular conductance.

**Discussion**

**Figure 3.** Changes in P0, peak aortic flow, and Zc. The greater reduction in P0 (P=0.002) with omapatrilat was a result of a greater reduction in Zc (P=0.001) with no change in peak flow. Values are mean±SEM. *P<0.05, paired change from baseline. †P<0.05, difference in paired change from baseline, omapatrilat versus enalapril.

**Figure 4.** Change in Zc according to quintiles of change in MAP. Group mean (±SEM) change in Zc is plotted as a function of average change in MAP for each quintile. ANOVA demonstrated no treatment-related differences in change in MAP (P=0.678). However, there was a significant effect of treatment on change in Zc (P=0.041) with no interaction between treatment and MAP quintile (P=0.963), indicating a parallel downward shift in the relationship between change in mean pressure and change in Zc after treatment with omapatrilat. Bottom, Number of subjects per group.
to ventricular ejection and minimize pulsatile load. Recent studies have shown that conduit vessel properties are subject to short-term, endothelium-dependent modulation.\textsuperscript{31–33} Omapatrilat is more effective than an ACE inhibitor at restoring endothelial function in animal models of hypertension.\textsuperscript{34} This may translate into better matching between blood flow and vessel properties and reduced pulsatile load.

It is important to note that NEP catalyzes the degradation of several vasoactive peptides, including vasodilators such as NPs, bradykinin, and substance P, and vasoconstrictors such as endothelin-1 and angiotensin-II.\textsuperscript{10,34} Therefore, the net effect of NEP inhibition on vascular tone depends on the balance between production and degradation of these competing vasoactive molecules. We have shown that dual NEP and ACE inhibition with the VPI omapatrilat resulted in a potent antihypertensive effect when administered as monotherapy.

Limitations of our study should be underscored. Omapatrilat monotherapy was more effective than enalapril monotherapy at reducing trough MAP. Thus, differences in stiffness parameters are partially attributable to differences in MAP. However, we have shown that even after adjusting for changes in MAP, the difference in $Z_c$ remained significant. Carotid-femoral PWV was reduced in both treatment groups, which raises the possibility of regression to the mean. However, we did not use any direct measure of arterial stiffness as an entry criterion for the study, making regression to the mean less likely.

Our observations raise the important and clinically relevant question of whether treatment specifically aimed at reducing central conduit vessel stiffness and pulse pressure will reverse the excess risk associated with higher pulse pressure, resulting in improved outcome as compared with agents that reduce only MAP with little or no effect on central conduit stiffness. Studies are needed to clarify the relative effects of various classes of antihypertensive agents on conduit and resistance vessel function. Potentially promising forms of therapy include nitrates, aldosterone antagonists, low-dose diuretics, and converting enzyme inhibitors combined with salt restriction or low-dose diuretics.\textsuperscript{8,35–36} On the basis of these mechanistic studies, it will be possible to design appropriate clinical end point trials that can test the hypothesis that reduction of conduit vessel stiffness represents a novel and clinically relevant therapeutic target in hypertension.

In summary, we have shown that VPI with omapatrilat, compared with ACE inhibition with enalapril, produced greater reductions in pulse pressure and proximal aortic stiffness, thereby reducing load on the ventricle during all phases of the ejection period. Additional studies are needed to assess the impact of these changes in pulsatile load on ventricular function and clinical events.

Appendix

Study Investigators: Gary F. Mitchell, Holliston, Mass, Principal Investigator; Yves Lacourcière, Ste Foy, Quebec; Jean-Pascal Ouellet, Sherbrooke, Quebec; Joseph Izzo, Buffalo, NY; Joel Neutel, Orange, Calif; Deanna Cheung, Long Beach, Calif; Melvin Tonkon, Santa Ana, Calif; L. Kent Smith and Kris Vijay, Phoenix, Ariz; J. Malcolm O, Arnold, London, Ontario; Jackson Wright, Cleveland, Ohio; Mark Dunlap, Cleveland, Ohio; Paul Conlin, Boston, Mass; Richard Ogilvie, Toronto, Ontario; William Smith, New Orleans, La; and Marc A. Pfeffer, Boston, Mass.

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