Changes in Aortic Stiffness and Augmentation Index After Acute Converting Enzyme or Vasopeptidase Inhibition

Gary F. Mitchell, Yves Lacourcière, J. Malcolm O. Arnold, Mark E. Dunlap, Paul R. Conlin, Joseph L. Izzo, Jr

Abstract—Augmentation index (AI), a measure of enhanced wave reflection, has been proposed as a bedside measure of aortic stiffness. However, because AI is potentially sensitive to various factors other than vessel wall stiffness, the utility of AI as a stiffness indicator may be limited. To assess relations between AI and vascular properties, we used arterial tonometry and aortic Doppler flow to evaluate trough (24 hours) and peak (4 hours) pulsatile hemodynamics and pulse wave velocity in 159 individuals with systolic hypertension at the completion of a 12-week period of monotherapy with the vasopeptidase inhibitor omapatrilat (80 mg; n=75) or the converting enzyme inhibitor enalapril (40 mg; n=84). Characteristic impedance (Zc) was calculated from the ratio of change in carotid pressure and aortic flow in early systole. Systolic ejection period (SEP), timing of wave reflection, and AI were assessed from the carotid waveform. Comparable acute reductions in mean pressure were associated with greater reductions in peripheral resistance with enalapril, whereas neither drug had an acute effect on Zc. Both drugs reduced AI, but neither drug altered the timing of wave reflection. Both drugs increased heart rate and shortened SEP. Multiple regression analysis demonstrated that the acute reduction in AI was most affected by reductions in SEP and peripheral resistance. Change in AI was inversely related to change in Zc, and pulse wave velocity did not enter the model. Our findings indicate that AI is a complex surrogate marker that is inversely related to changes in proximal aortic stiffness in systolic hypertension. (Hypertension. 2005; 46:1111-1117.)

Key Words: angiotensin converting enzyme ■ aorta ■ clinical trials ■ hypertension ■ pulse

High pulse pressure is now recognized as an important cardiovascular disease risk factor for myocardial infarction, stroke, and development and progression of heart failure, even after adjusting for the effects of other known cardiovascular disease risk factors. Elevated pulse pressure in elderly and hypertensive individuals is attributable to increased aortic stiffness and wave reflection. Because of the excess risk associated with elevated pulse pressure, there is considerable interest in defining interventions that reduce aortic stiffness, especially in individuals with systolic hypertension. There is a commensurate level of interest in defining methods to assess the effects of interventions on aortic stiffness.

Augmentation index (AI) determined from either a directly measured or a derived central arterial pressure waveform has been proposed as a measure of aortic stiffness and wave reflection. AI is the percentage of central pulse pressure attributable to the secondary systolic pressure rise produced by the overlap of the forward and reflected pressure waves. Three major factors influence wave reflections: the distance to the reflecting site, the speed of wave transmission, and the magnitude of the reflection coefficient. Wave reflections arise in regions of impedance mismatch in the arterial tree and combine to produce a relatively discrete global reflected wave that appears to have arisen from a single junction, or “effective” reflecting site. When the distance to reflecting sites is short or pulse wave velocity (PWV) is high, the reflected wave arrives in the proximal aorta prematurely, during early systole, leading to a secondary systolic pressure peak and increased central pulse pressure.

Because of the dependence of timing of wave reflection on PWV, reductions in AI after an intervention have been interpreted as evidence of comparable reductions in PWV and aortic stiffness. However, AI also depends on other variables such as heart rate, systolic ejection period (SEP), and peripheral vasoconstriction, which can change considerably in the absence of any change in aortic stiffness. The resulting complex relations between AI and aortic stiffness have generated considerable controversy in the literature regarding the usefulness of AI as a surrogate measure of arterial stiffness. With advancing age, aortic stiffness increases markedly whereas peripheral arterial stiffness changes very
little. As aortic stiffness reaches or exceeds peripheral arterial stiffness, the impedance mismatch between aorta and periphery is reduced. The resulting reduction in the arterial impedance gradient would be expected to reduce wave reflection and shift reflecting sites distally, potentially leading to an inverse relation between aortic stiffness and AI. For these reasons, relations between changes in AI and aortic stiffness after an intervention are unpredictable.

Converting enzyme inhibition has been shown to reduce AI in hypertensive individuals. As previously reported, the Conduit Hemodynamics of Omapatrilat International Research (CHOIR) study evaluated changes in pulsatile hemodynamics after 12 weeks of converting enzyme inhibition with enalapril or dual converting enzyme and neutral endopeptidase inhibition with omapatrilat. A secondary goal of the CHOIR study was to evaluate the acute-on-chronic effects of study medication after the final dose of study medication to identify any short-term functional effects on arterial properties including AI. Therefore, we evaluated in detail the relations between changes in aortic stiffness and AI after an acute drug intervention.

Methods
Men and women 18 years of age or older were eligible for the trial if they were in sinus rhythm and had moderate systolic or mixed systolic–diastolic hypertension, defined as a seated systolic blood pressure \( \geq 160 \text{ mm Hg} \) and \( \geq 200 \text{ mm Hg} \) and a seated diastolic blood pressure \( \leq 110 \text{ mm Hg} \) at the time of the qualifying visit. Heart failure, documented ejection fraction \( <45\% \), valvular heart disease, or clinically significant peripheral vascular disease were exclusion criteria. Additional exclusion criteria have been presented in detail elsewhere. An institutional review board at each clinical center approved the study protocol and each participant 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 \( \geq 160 \text{ mm Hg} \) and \( \geq 200 \text{ mm Hg} \) and the diastolic blood pressure \( \leq 110 \text{ mm Hg} \). 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 and 10:00 AM with the patient in a fasting state before using 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. Treatment was initiated with either 10 mg omapatrilat or 10 mg enalapril and was titrated at 2 and 4 weeks to doses of 40 then 80 mg omapatrilat or 20 then 40 mg enalapril. Patients who did not 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 previous dose of study medication, under identical conditions as the baseline study. A final dose of study medication was then administered and followed by a repeat hemodynamic study 4 hours later.

Hemodynamic Data Acquisition
Details of the hemodynamic protocol and data analysis have been reported. Briefly, participants were evaluated in the supine position after \( \approx 10 \) minutes of rest. Supine auscultatory blood pressures were obtained by using a custom-made, computer-controlled device that automatically inflated the cuff to a user-preselect maximum pressure and then controlled deflation at 2 mm Hg/s. This device recorded ECG, cuff pressure, and cuff microphone signal throughout the blood pressure acquisition, thus allowing for over-read of all blood pressures. Arterial tonometry with ECG (10 seconds at each site) was obtained from the brachial, radial, femoral, and carotid arteries using a transducer that was custom-made by Cardiovascular Engineering, Inc. This transducer has a small sensor surface area and a frequency response that is flat into the kHz range. Left ventricular outflow tract diameter and flow were measured by echocardiography. Body surface measurements from suprasternal notch to waveform recording sites were obtained. All clinical sites underwent a rigorous training and certification procedure under the direction of the core laboratory (Cardiovascular Engineering, Inc) before enrolling any participants into the trial. All data were digitized during the primary acquisition, transferred to CD-ROM and shipped to the core laboratory for analysis.

Data Analysis
Tonometry waveforms were signal-averaged using the ECG as the fiducial point. Average systolic and diastolic cuff pressures were used to calibrate peak and trough of the signal-averaged brachial waveform. Diastolic and mean brachial pressures were then used to calibrate carotid, radial, and femoral waveforms. Carotid–femoral and carotid–radial PWV, true and apparent pressure amplification, input impedance, and \( Z_0 \) were calculated as previously described. The first impedance modulus was obtained from the input impedance spectrum, which was calculated using Fourier transforms of pressure and flow. AI was assessed from the carotid pressure waveform. Forward (\( P_f \)) and reflected or backward (\( P_b \)) wave amplitudes were calculated from the pressure and flow waveforms. To explore expected effects of changes in central and peripheral arterial properties on wave reflection, a hypothetical global reflection coefficient \( = (Z_c - Z_0)/(Z_c + Z_0) \) was calculated from \( Z_c \) and peripheral resistance \( Z_0 \), assuming a single reflecting site. As previously reported, reproducibility of measures of central aortic stiffness using our protocol in a multicenter setting is high, with intraclass correlation coefficients of 0.93 to 0.95 for repeated measures of central hemodynamic variables, such as cardiac output and \( Z_0 \).

Statistical Analysis
Baseline characteristics were tabulated and compared using a \( \chi^2 \) statistic for dichotomous variables and analysis of variance for continuous 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 for continuous variables were assessed by a general linear model that adjusted for baseline values. Stepwise multivariable regression was then used to evaluate relations between change in AI and changes in its various potential determinants. Values are presented as the mean±SEM. A 2-sided \( P<0.05 \) was considered significant.

Results
As noted in our previous publication, 335 participants were enrolled into the pretreatment phase of the study, 213 completed the single-blind lead-in period, met entry criteria, and were randomized to active treatment; 185 completed the double-blind active treatment period and 167 had technically adequate tones hemodynamics at the completion of the 12-week treatment period. Of these 167 candidates who were eligible for inclusion in the acute study, 159 had technically adequate paired assessments of hemodynamics before and 4 hours after the final dose of study medication. Of the 8 participants who could not be evaluated 4 hours after dose, 7 participants (3 assigned to enalapril and 4 assigned to omapatrilat) had technically inadequate hemodynamic studies, and 1 participant (assigned to omapatrilat) was unable to complete the 4-hour study because of personal reasons. Importantly, all decisions regarding data quality were made before unblinding of treatment codes. Baseline characteristics
of the treatment groups are presented in Table 1. The groups were comparable although there were trends toward lower body weight and a higher percentage of diabetic patients in the omapatrilat group (Table 1).

Pulsatile hemodynamic variables are presented in Tables 2 and 3. The drugs produced comparable acute reductions in central and peripheral systolic and mean arterial pressure. However, enalapril produced a greater reduction in diastolic pressure that blunted the reduction in central and peripheral pulse pressure. Both drugs reduced central pulse pressure more than peripheral pulse pressure (Table 2). As a result, apparent amplification increased in both groups, although true amplification remained unchanged (Table 3). Enalapril reduced peripheral resistance more than omapatrilat and increased cardiac output. Both drugs increased heart rate and reduced the first modulus of impedance but neither drug had a significant effect on Zc (enalapril, \( P = 0.10 \); omapatrilat \( P = 0.99 \)) (Figure 1). The drugs had comparable modest effects on carotid–radial and carotid–femoral PWV, although the reduction in carotid–femoral PWV with omapatrilat did not achieve statistical significance (\( P = 0.060 \)).

AI was markedly reduced in both groups (Table 3 and Figure 2), as was the global reflection factor (\( P_0/P_1 \)) (Table 3). Neither drug had an effect on timing of wave reflection, whereas both drugs shortened the SEP and thereby reduced temporal overlap between forward and reflected waves (Table 3). Correlations between change in AI and changes in various potential determinants of AI are presented in Table 4. Relations between these variables and change in AI differed by treatment group only for \( Z_c \) (\( P = 0.017 \)). Change in carotid–femoral PWV was related to change in augmentation only in the omapatrilat group, although the difference between treatment groups was not significant (\( P = 0.37 \)).

Stepwise linear regression analysis was used to evaluate change in AI as the dependent variable and changes in the variables in Table 4 as independent variables. The global reflection factors were not included as covariates because they are closely related to the other variables. Models were computed separately by treatment group (Table 5). Regression coefficients varied modestly between groups, although only the regression coefficient for \( Z_c \) differed by treatment (\( P = 0.044 \)). Carotid–femoral PWV did not enter the model for either treatment group. The regression coefficient for change in \( Z_c \) was negative in each treatment group, indicating that a reduction in \( Z_c \) was associated with an increase in AI (Table 5 and Figure 3). We used the treatment-specific regression coefficients presented in Table 5 to estimate the contribution of the change in each independent variable to the observed change in AI. Net reductions in AI were largely attributable to reductions in SEP and peripheral resistance,
with greater contributions from change in SEP in the omapatrilat group and change in peripheral resistance in the enalapril group (Table 5). Thus, in this hypertensive sample after converting enzyme or vasopeptidase inhibition, reductions in AI were related to shortening of the SEP and reduced peripheral resistance rather than a change in aortic stiffness as assessed by $Z_c$ or carotid–femoral PWV.

**Discussion**

This study evaluated the acute pulsatile hemodynamic effects of converting enzyme inhibition with enalapril as compared with dual converting enzyme and neutral endopeptidase inhibition with omapatrilat. Both drugs reduced mean arterial pressure and measures of pulsatile hemodynamic load, including AI. However, the reduction in AI was not attributable to a reduction in aortic stiffness, as assessed by $Z_c$ or carotid–femoral PWV. Instead, reductions in AI were principally related to a reduction in peripheral resistance, which decreases the amplitude of the reflected wave, and shortening of SEP, which decreases temporal overlap between forward and reflected waves. In multivariable models, change in AI was inversely related to change in proximal aortic stiffness ($Z_c$) and was unrelated to change in carotid-femoral PWV. Thus, in this middle-aged to elderly hypertensive sample, change in AI was an unreliable surrogate marker for change in aortic stiffness after inhibition of angiotensin-converting enzyme alone or in combination with inhibition of neutral endopeptidase.

Several recent studies provide additional support for the observation that AI may be an unreliable measure of aortic stiffness in various settings. Changes in AI and carotid–femoral PWV with advancing age were evaluated in a healthy subset of the Framingham offspring cohort. Carotid–femoral PWV and forward wave amplitude, which are related to aortic stiffness, were shown to increase continuously with advancing age. In contrast, AI increased in middle-aged individuals and then plateaued (in men) or declined (in women) beyond 60 years of age despite a continued increase in carotid–femoral PWV. Thus, in these older individuals, AI failed to detect the progressive increase in aortic stiffness with advancing age. A cross-sectional comparison of AI in diabetic and nondiabetic individuals found no difference in AI between groups even though carotid–femoral PWV was elevated in the diabetic group. Another study evaluated change in AI during infusion of a $\beta$-adrenergic agonist in healthy volunteers. AI decreased during the infusion whereas peripheral pulse pressure increased and carotid–femoral PWV was unchanged. Thus, data from both cross-sectional and interventional studies have shown that AI has a highly variable relation to aortic stiffness, including an inverse relation in some settings.

The basis for an inverse relation between changes in proximal aortic stiffness and augmentation index is apparent from an analysis of the physical principles governing wave reflection at arterial discontinuities. The local reflection ratio, R, at an arterial discontinuity is given by the expression:

$$ R = \frac{P_R}{P_F} = \frac{R}{1 + R} $$

![Figure 1](https://hyper.ahajournals.org/) Changes in pulsatile hemodynamic load after enalapril or omapatrilat. $Z_c$ was unchanged after either drug, whereas the first modulus of impedance decreased significantly in both groups. Total arterial compliance was increased after enalapril, whereas the change after omapatrilat was not significant. Because $Z_c$ was unchanged in both groups, the reduction in the first modulus of impedance was a manifestation of reduced systolic wave reflection and increased peripheral arterial compliance. $^\ast P<0.05$ for within group change from baseline.
abrupt increase in arterial stiffness between aorta and muscular arteries creates a reflecting site that is relatively close to the heart. However, aortic PWV is substantially lower in these individuals (4 to 6 m/s) as compared with middle-aged and older adults, in whom carotid–femoral PWV is often 10 to 20 m/s. As a result, the reflected wave arrives in late systole and extends into early diastole in young adults, despite the relative proximity of a dominant reflecting site. As the aorta stiffens in young adults, PWV increases and wave reflections arrive earlier. However, by 60 years of age, aortic stiffness has risen sufficiently that the effects of increasing PWV on timing of wave reflection are eclipsed by the marked reduction in stiffness gradient between central and peripheral arteries, which reduces the amplitude of the reflected wave. In the present study in a middle-aged hypertensive sample, carotid–femoral PWV was greater than carotid–radial PWV, indicating reversal of the stiffness gradient to at least the level of the radial artery. Loss of the normal stiffness gradient would be expected to reduce wave reflection in this transition zone from aorta to radial artery. Properties of small arteries and resistance vessels, which are the next major step-up in arterial impedance, will therefore have a dominant effect on wave reflection, as we have shown.

In young adults, Zc and PWV in the aorta are normally much lower than values found in the muscular arteries. The

![Figure 2. Changes in wave reflection and augmentation. Both drugs substantially reduced AI while having no effect on the timing of wave reflection. The global reflection factor and SEP were reduced by both drugs, with omapatrilat having a greater effect on SEP despite a comparable increase in heart rate. *P<0.05 for within-group change from baseline. †P<0.05 for between-group change from baseline.](image)

**TABLE 4. Correlates of Change in AI**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Enalapril</th>
<th>Omapatrilat</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_a/P_p$, amplitude ratio (%)</td>
<td>0.65</td>
<td>0.46</td>
</tr>
<tr>
<td>$(Z_c - Z_d)/(Z_c + Z_d)$ (no units)</td>
<td>0.66</td>
<td>0.37</td>
</tr>
<tr>
<td>Reflected wave arrival time (ms)</td>
<td>-0.57</td>
<td>-0.58</td>
</tr>
<tr>
<td>SEP (ms)</td>
<td>0.45</td>
<td>0.48</td>
</tr>
<tr>
<td>Peripheral resistance (DSC)</td>
<td>0.32</td>
<td>0.41</td>
</tr>
<tr>
<td>$Z_c$ (DSC)</td>
<td>-0.35</td>
<td>0.04*</td>
</tr>
<tr>
<td>Carotid-femoral PWV (m/s)</td>
<td>0.08</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*P<0.05 for between-group difference.

**TABLE 5. Multivariable Correlates of Change in AI**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Enalapril</th>
<th>Omapatrilat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflected wave arrival time (ms)</td>
<td>-0.239±0.031</td>
<td>-0.2±0.6</td>
</tr>
<tr>
<td>SEP (ms)</td>
<td>0.146±0.042</td>
<td>-3.2±0.3</td>
</tr>
<tr>
<td>$Z_c$ (DSC)</td>
<td>-0.122±0.017</td>
<td>1.1±0.7</td>
</tr>
<tr>
<td>Peripheral resistance (DSC)</td>
<td>0.012±0.002</td>
<td>-3.3±0.5</td>
</tr>
</tbody>
</table>

*P for difference between therapies in the amount of change in AI attributable to each independent variable.
AI) will be a valuable marker of clinical risk, because the appropriate long-term follow-up studies with clinical end points in a generalizable population sample have not been performed. However, we can say that if AI or change in AI is shown to be related to clinical risk, it will be necessary to assess arterial stiffness by another means (for example PWV) to determine whether a change in arterial stiffness contributed to the beneficial or adverse effect.

Potential limitations of our study merit consideration. We did not use a washout period between the long-term and acute phases of the study. However, as previously presented, both drugs reduced AI modestly and comparably during the initial 12-week monotherapy phase of the study (from 25% to 21% for enalapril and from 24% to 19% for omapatrilat). Thus, despite 12 weeks of antecedent therapy, the acute (trough-to-peak) relative reduction in AI reported herein was approximately twice as large as the long-term (trough-to-trough) effect for both drugs. Thus, most of the effect of angiotensin-converting enzyme or vasopeptidase inhibition appears to be acute and functional rather than long-term or structural. Given that most of the reduction in AI is acute and that the long-term effect of the 2 drugs on AI was comparable, we believe that the results would have been substantially similar had the acute phase been preceded by a washout period.

A recent review has suggested that failure to properly identify the inflection point between forward and reflected wave could lead to overestimation of Zc assessed in the time domain and underestimation of AI. As detailed in a previous publication, our calculation of Zc is not dependent on identification of the inflection point in the upstroke of the carotid pressure wave (see Figure 1). Furthermore, as noted in the previous report, Zc assessed in the time domain is highly correlated with Zc assessed in the frequency domain. For example, in the trough studies of the present sample, the correlation between Zc assessed as the average of impedance harmonics 2 to 10 versus Zc assessed in the time domain was 0.967 (P<0.001). Therefore, it is unlikely that errors in identification of the inflection point in the pressure waveform affected calculation of Zc. Improper alignment of pressure and flow waveforms represents another potential source of error for Zc calculated in the time domain, whereas Zc calculated in the frequency domain is not affected by alignment errors. The high degree of correlation between time and frequency domain estimates of Zc indicates that the method we used to realign the foot of the pressure and flow waveforms was highly accurate. We used SEP in the multivariable AI models because it is SEP that determines the extent of overlap between forward and reflected wave. However, substantially similar results were obtained if heart rate was used instead of SEP, except that change in AI was inversely related to change in heart rate.

Perspectives
AI depends on timing and amplitude of the reflected pressure wave. However, the location of the reflecting sites and the amplitude of the reflected wave depend on the arterial stiffness gradient between central aorta and periphery. When aortic stiffness approaches or exceeds proximal muscular artery stiffness, proximal wave reflection is diminished and reflecting sites shift distally in the arterial system, resulting in little change in timing of wave reflection despite the associated increase in PWV. As a result, AI is rendered increasingly sensitive to changes in distal arterial properties. Previous studies have suggested that increased AI may be associated with increased cardiovascular risk, suggesting that a reduction in AI may be desirable. However, various means for reducing AI may not have equivalent effects on clinical outcome. Wave reflection limits transmission of pressure pulsatility into the periphery. Therefore, an intervention that reduces wave reflection necessarily increases pressure transmission and may have unanticipated and potentially untoward effects in the microcirculation, which may limit clinical benefit. In future cross-sectional and interventional studies that use AI as a measure of pulsatile load, each of the several determinants of AI should be assessed to clarify the pathophysiology of adverse associations and the mechanism of favorable effects of various interventions.

Acknowledgments
This study was funded by a grant from Bristol-Myers Squibb Pharmaceutical Research Institute.

References


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Hypertension. 2005;46:1111-1117; originally published online October 17, 2005;
doi: 10.1161/01.HYP.0000186331.47557.ae
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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