LEFT VENTRICULAR RESPONSES TO ACUTE CHANGES IN LATE SYSTOLIC PRESSURE AUGMENTATION IN OLDER ADULTS

Nancy K. Sweitzer,1 Scott J. Hetzel,2 Joseph Skalski,1,3 Mauricio Velez,1,4 Kevin Eggleston,1,5 and Gary F. Mitchell6

BACKGROUND
Changes in the cardiovascular system with age may predispose older persons to development of heart failure with preserved ejection fraction. Vascular stiffening, aortic pressure augmentation, and ventricular–vascular coupling have been implicated. We explored the potential for acute reductions in late systolic pressure augmentation to impact left ventricular relaxation in older persons without heart failure.

METHODS
Sixteen older persons free of known cardiovascular disease with the exception of hypertension had noninvasive tonometry and cardiac ultrasound to evaluate central augmentation index (AI) and diastolic function at baseline and after randomized, blinded administration of intravenous B-type natriuretic peptide (BNP) and hydralazine in a crossover design.

RESULTS
AI was significantly reduced after BNP (11.4 ± 8.9 to –0.2 ± 14.7%; P = 0.02) and nonsignificantly reduced after hydralazine (14.7 ± 8.4% to 11.5 ± 8.8%; P = 0.39). With decreased AI during BNP, a trend toward worsened myocardial relaxation by tissue Doppler imaging occurred (E′ velocity pre- and post-BNP: 10.0 ± 2.5 and 8.8 ± 2.0 cm/s, respectively; P = 0.06). There was a significant fall in stroke volume with BNP (68.5 ± 18.3 to 60.9 ± 18.1 ml; P = 0.02), suggesting that changes in preload overwhelmed effects of afterload reduction on ventricular performance. With hydralazine, neither relaxation nor stroke volume changed.

CONCLUSIONS
Acute changes in late systolic aortic pressure augmentation do not necessarily lead to improved systolic or diastolic function in older people. Preload may be a more important determinant of cardiac performance than afterload in older people with compensated ventricular function. The potential for changes in preload to impair rather than enhance left ventricular systolic and diastolic function in older people warrants further study.

CLINICAL TRIALS REGISTRATION
This study is registered at clinicaltrials.gov as NCT00204984.

Keywords: arterial stiffness; arterial wave reflection; blood pressure; cardiac performance; hypertension.

doi:10.1093/ajh/hpt043

Alterations in arterial stiffness and resultant late systolic pressure augmentation are primary contributors to isolated systolic hypertension of the elderly. The pattern of late systolic pressure augmentation commonly seen with aging may impact left ventricular performance in the elderly and predispose to development of cardiovascular disease.1,2 As humans age and arteries stiffen, small vessel changes lead to increases in peripheral vascular resistance, whereas large vessel stiffening causes increases in pulse wave velocity and late systolic pressure augmentation.3 Increased pressure in the proximal aorta in late systole results in abnormal left ventricular loading with aging.4–6 Increases in forward wave amplitude and relative wave reflection are hypothesized to contribute to isolated systolic hypertension in the elderly,7 although this pattern of late systolic pressure augmentation is also consistent with a change in reservoir function of the aorta due to central arterial stiffening. Central late systolic pressure augmentation is particularly prominent in women because of their short stature and has been hypothesized to contribute to left ventricular hypertrophy and increased population-attributable risk of heart failure among women.8

Although multiple indices of arterial stiffening have been proposed, the optimal means of describing load on the left ventricle continues to be debated.9,10 Late systolic pressure augmentation, often expressed as augmentation index (AI), may contribute significantly to central pulse pressure and can be rapidly modified pharmacologically. In animal models, late systolic loading of the heart has been shown to decrease stroke volume and slow myocardial relaxation.11 Thus, a decrease in AI may improve left ventricular stroke...
volume and ventricular relaxation, perhaps increasing cardiac output and opening new therapeutic avenues for treatment of cardiovascular disease in the elderly. The purpose of this study was to investigate the impact of acute changes in arterial pressure augmentation on ventricular performance in elderly persons without diagnosed cardiovascular disease, with the exception of hypertension. Our hypothesis was that decreased late systolic augmentation would result in improved left ventricular relaxation and increased stroke volume in elderly participants.

Wave travel in the proximal aorta was perturbed acutely by infusions of nesiritide (Janssen Pharmaceuticals, Titusville NJ) and hydralazine. Nesiritide is recombinant human B-type natriuretic peptide (BNP). BNP binds to the particulate guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to increased intracellular concentrations of guanosine 3’5’-cyclic monophosphate and smooth muscle cell relaxation. In animal models and human studies, natriuretic peptide administration leads to both arterial and venous dilation without significant cardiac effects. When used clinically in patients with heart failure and systolic left ventricular dysfunction, arterial vasodilation appears to predominate and is accompanied by a mild natriuresis. Hydralazine is a phthalazine vasodilator that acts on arteriolar smooth muscle without affecting coronary arteries or venous smooth muscle. Because its effect is at the level of the arterioles, hydralazine exerts its blood pressure effect through changes in peripheral resistance, with less prominent effects on central pressure augmentation. In this study, intravenous hydralazine and BNP were administered to elderly persons at doses producing comparable effects on systemic vascular resistance to examine acute effects of the resultant arterial dilation and changes in late systolic pressure augmentation on left ventricular systolic and diastolic performance.

**METHODS**

**Study sample**

Participants were recruited through 2 mechanisms. Most were identified using a database housed in the University of Wisconsin Institute on Aging of individuals aged ≥65 years interested in participating in research studies. An additional, smaller group of participants responded to posted flyers. Seventeen older volunteers free of known cardiovascular disease were studied (aged ≥65 years). Known or suspected coronary artery disease, left ventricular dysfunction, significant valvular, infiltrative, pericardial, or congenital heart disease, or resting systolic blood pressure <100 mm Hg were exclusion criteria. Participants with hypertension (defined as a previous recorded BP >140 mm Hg systolic or >90 mm Hg diastolic or current use of antihypertensive medications) were included, although if they arrived for the study visit off medications for 48 hours and with a systolic blood pressure >200 mm Hg, they were not studied. Five patients were receiving lipid-lowering therapy. Two patients had a diagnosis of type 2 diabetes mellitus without evidence of end-organ involvement. All participants were required to have an ejection fraction >55% without regional wall motion abnormalities based on visual assessment by an experienced echocardiographer (N.K. Sweitzer). Ejection fraction was not quantified for this study. Participants were to be excluded if they had a serum creatinine on the day of study >2 mg/dl. The study was not powered to examine sex differences in responses to changes in AI. The protocol was approved by the University of Wisconsin Human Subjects Committee, and each participant gave written informed consent before participation.

**Study protocol**

The study was performed at the Clinical and Translational Research Center of the University of Wisconsin Hospital under standardized conditions. Hypertensive participants were asked to hold prescribed antihypertensive medications for 48 hours before each study session. Upon arrival, intravenous access was obtained, and blood was drawn for laboratory analysis. Renal function was assessed using the standard clinical assay for serum creatinine. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) equation. After at least 20 minutes of quiet rest, baseline blood pressure was obtained using a semiautomated, computer-controlled cuff by repeating auscultation at 2-minute intervals with a goal of obtaining 3 sequential readings within 5 mm Hg for both systolic and diastolic blood pressure, after which baseline arterial hemodynamics and echocardiographic images were obtained. After acquisition of the baseline data, participants received an infusion of either nesiritide (1 mcg/kg bolus followed by 0.005 mcg/kg/min continuous infusion) or hydralazine (10 mg bolus, followed by placebo infusion), in a cross-over design, randomized, double-blinded fashion. Doses were chosen based on preliminary dose-finding studies performed to select doses with discernible and similar effects on peripheral resistance (unpublished data). Ten or more minutes after start of the continuous infusion, repeat arterial hemodynamics were obtained. Participants received each of the 2 drugs in separate sessions that were at least 2 weeks apart. At each visit, participants received both a bolus and an infusion.

**Data acquisition**

Participants were studied supine after quiet rest using previously described methods. Auscultatory blood pressure was obtained using a semiautomated, computer-controlled cuff and used for calibration of tonometric waveforms. Arterial tonometry was obtained from the brachial, radial, femoral, and carotid arteries in quick succession with a custom transducer (Cardiovascular Engineering, Norwood, MA). Simultaneous limb-lead electrocardiography was used for temporal alignment of data. A limited echocardiogram was performed to allow for quantification of mitral inflow, mitral annular relaxation velocity, and left ventricular outflow tract diameter and flow. Body surface measurements were assessed from suprasternal notch to brachial, radial, femoral, and carotid recording sites. Data were digitized during the primary acquisition, transferred to CD-ROM, and shipped to Cardiovascular Engineering for analysis.
Data/statistical analysis

The primary parameter of interest in this analysis was the association between late systolic pressure augmentation, as measured by AI, and myocardial diastolic performance, as measured by lateral annular mitral velocity (E’), a measure of early diastolic myocardial relaxation. Tonometry waveforms were analyzed as described previously. Briefly, all arterial pressure waveforms were signal-averaged using the R-wave of the electrocardiogram as the fiducial point. The signal-averaged brachial waveform was calibrated to cuff systolic and diastolic pressures. AI was measured from the signal-averaged carotid waveform as previously described. Peak early (E) and late (A) diastolic mitral flow velocities were measured from the pulse wave Doppler mitral inflow signal collected in the apical 4-chamber view. Left ventricular outflow tract diameter was measured from 2-dimensional images in the parasternal long-axis view and used to compute cross-sectional area for conversion of flow velocities to volumes. Lateral annular mitral velocity (E’) was calculated from the mean amplitude of early diastolic peaks in a 20-second recording of tissue Doppler spectra from the lateral mitral annulus, measured in triplicate by 3 independent, blinded observers. Arterial elastance was calculated as end-systolic pressure (derived from central tonometry) divided by stroke volume determined by Doppler echocardiography.

Normality of the distributions of all variables was assessed through visual interpretation of the histograms before conducting the analysis. All variables showed normal distribution. AI and E’ were compared before and after drug administration using paired t tests adjusted for multiple comparisons using the Holm adjustment. In addition, an adjusted repeated measures analysis of variance was run on AI and E’ in which we controlled for heart rate as a covariable. The parameter of interest was the association between AI and E’ and was assessed with linear regression and Pearson correlation testing. Classical assumptions of linear regression analysis were satisfied, including normal distribution of the variables of interest. Descriptive variables are presented for purposes of giving a complete picture of the cardiovascular properties of the subjects without correction for multiple comparisons. All t tests were 2-sided with α = 0.05.

RESULTS

Seventeen volunteers aged ≥ 65 years years signed informed consent. At the initial study visit, screening procedures were performed, including measurement of blood pressure and serum creatinine and a brief screening echocardiogram to determine eligibility. No participant failed the screening; the highest recorded systolic blood pressure was 172 mm Hg, the highest creatinine measurement was 1.3 mg/dl (estimated glomerular filtration rate = 57 ml/min/1.73m²), and all subjects had an ejection fraction > 55%. Of the seventeen subjects enrolled, all participated in at least 1 study visit with drug infusion; 16 (8 women) had interpretable arterial stiffness data and form the sample reported here (Table 1). Seven participants had a history of hypertension treated with antihypertensive medication. Systolic blood pressure at baseline in these persons was 155 ± 26 mm Hg (mean ± SD), and diastolic blood pressure was 71 ± 7 mm Hg. Of the 9 participants without known hypertension, systolic blood pressure at baseline was 125 ± 17 mm Hg, and diastolic blood pressure was 63 ± 5 mm Hg. All antihypertensive medications were held for at least 48 hours before each study visit. Complete hemodynamic data for both BNP and hydralazine were obtained in 13 of the 17 participants, with data available for BNP in 14 participants and for hydralazine in 15 participants.

The impact of BNP and hydralazine on the primary parameters of interest is shown in Table 2. Both drugs produced modest vasodilation with comparable and significant reductions in peripheral resistance. BNP infusion significantly reduced AI. In contrast, hydralazine had a minimal effect on the central pressure waveform, despite a comparable decrease in peripheral resistance. There was a weak negative relation between AI and E’, which was not statistically significant (R = −0.12; R² = 0.013; P = 0.22), indicating that decreased augmentation was not associated with improvement in this measure of ventricular relaxation. Heart rate increased with administration of both drugs (Table 3); however, the change in AI with BNP infusion remained significant after adjustment for heart rate (P = 0.02).

The effects of BNP and hydralazine on peripheral and central blood pressure and other markers of central hemodynamics are shown in Table 3. BNP reduced brachial mean and systolic pressure, whereas hydralazine had no effect.

Table 1. Demographic characteristics of the study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>16</td>
</tr>
<tr>
<td>Age, years</td>
<td>70.2 (67.9–73.8)</td>
</tr>
<tr>
<td>Female/Male, No.</td>
<td>8/8</td>
</tr>
<tr>
<td>Hypertension, No.</td>
<td>7</td>
</tr>
<tr>
<td>Diabetes, No.</td>
<td>2</td>
</tr>
<tr>
<td>Baseline creatinine, mg/dl</td>
<td>0.90 (0.80–1.03)</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>76 (69–87)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.0 (72.3–80.7)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.9 (161.3–174.6)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.0 (24.9–28.6)</td>
</tr>
<tr>
<td>Lipid-lowering therapy, No.</td>
<td>5</td>
</tr>
<tr>
<td>Tobacco use, No.</td>
<td>0 current, 6 former</td>
</tr>
<tr>
<td>Antihypertensive drug therapy, No.</td>
<td>3</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>2</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>2</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>1</td>
</tr>
<tr>
<td>Alpha blocker</td>
<td>1</td>
</tr>
<tr>
<td>Multidrug therapy</td>
<td>2</td>
</tr>
</tbody>
</table>

Data are displayed as median and interquartile range unless otherwise noted.
Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; eGFR, estimated glomerular filtration rate.
Pulse wave velocity increased comparably with both drugs and significantly during BNP infusion but was no longer significant after adjustment for the increase in heart rate, which is known to affect pulse wave velocity.\textsuperscript{19,20} Arterial elastance was not altered by either drug (BNP: 1.8 to 1.7 mm Hg/ml, \( P = 0.16 \); hydralazine: 1.7 to 1.6 mm Hg/ml, \( P = 0.32 \)). Both drugs shortened systolic ejection period, although BNP administration did so to a greater extent.

Cardiac responses to study drug administration are detailed in Table 4. BNP infusion was associated with a fall in stroke volume, whereas stroke volume was unchanged with hydralazine. When left ventricular filling was analyzed, early mitral inflow (E wave) velocity was decreased after BNP administration and unchanged with hydralazine.

**DISCUSSION**

In this study of hemodynamic responses to altered central arterial pressure in older persons, vasodilation with intravenous BNP, a simultaneous arterial and venous vasodilator, was associated with a significant decrease in AI. Hydralazine, an arteriolar dilator only, in contrast, did not reduce AI to the same extent. Although both drugs decreased peripheral resistance, BNP had a greater effect on both central and peripheral blood pressure. Measures of central arterial stiffness, including carotid–femoral pulse wave velocity, characteristic impedance, and arterial elastance did not improve with administration of either drug. Contrary to expectations, the decrease in central arterial pressure with BNP was not accompanied by an improvement in cardiac performance but rather by a fall in stroke volume and slight worsening of echocardiographic indices of left ventricular filling and relaxation, whereas these parameters were unchanged by hydralazine. Heart rate increased with administration of both drugs.

The fall in stroke volume and decreased late systolic pressure augmentation with BNP in this sample of older people without known heart disease suggests that competing pathophysiologic effects are involved. Although we had hypothesized that central arterial changes such as those seen with BNP, with a decrease in late systolic pressure augmentation, would be associated with improved diastolic function and increased stroke volume, the opposite occurred. The different effects of the 2 drugs on AI appear to reflect the fall in stroke volume with BNP administration. A fall in stroke volume indicates either a decrease in ventricular contractility or a decrease in preload. Because prior data suggest that BNP does not affect ventricular contractility, we hypothesize that changes in preload with BNP in our sample overwhelmed potentially favorable effects of decreased late systolic pressure augmentation on ventricular performance, which would tend to increase stroke volume. Although venous pressure was not measured invasively in our study, preload likely fell with BNP, as evidenced by the reduction in the echocardiographic E wave, the shortened systolic ejection period, and the known effects of BNP on preload. These data suggest that acute changes in venous hemodynamics and preload, or...
ventricular contractility, may have equal or greater effects on stroke volume as acute changes in arterial properties in older patients, particularly in the presence of age-related arterial and ventricular stiffening. This conclusion is supported by data from Sagawa et al. that demonstrated that at physiological heart rates, total arterial elastance and preload are more important determinants of stroke volume than arterial compliance, provided input impedance is unchanged. In our study, arterial elastance was not changed significantly by either drug treatment despite the change in AI. Careful consideration of invasively obtained left ventricular pressure–volume curves provides a possible explanation for the phenomenon we observed (i.e., a drop in stroke volume when preload and late systolic loading are simultaneously reduced). The end-diastolic pressure volume relation is markedly less steep than the end-systolic pressure volume relation in normal hearts. Therefore, even modest changes in end-diastolic pressure may have a greater effect on stroke volume than large changes in end-systolic pressure (the parameter most affected by pressure augmentation), as illustrated in Figure 1. Changes in the slopes of the end-systolic and end-diastolic pressure–volume relations will alter this interdependence. Although we did not directly measure preload in this study, this provides at least a theoretical explanation for the failure of a reduction in late systolic pressure augmentation to lead to improved cardiac output through improved ventricular–vascular interaction.

Our data reinforce the view that AI is not a reliable marker of central arterial stiffness and should not be used in clinical decision making about therapies affecting arterial properties. Our data demonstrate that changes in ventricular performance may have significant effects on AI. In addition, more direct measures of arterial stiffness, such as pulse wave velocity and aortic characteristic impedance, were not reduced in these participants despite the fall in AI, suggesting that AI is measuring something other than arterial properties. For example, a reduction in stroke volume after a drop in preload may result in a decrease in augmentation in the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>BNP</th>
<th>P value</th>
<th>Baseline</th>
<th>Hydralazine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral E wave, cm/s</td>
<td>67.0±10.5</td>
<td>58.1±8.2</td>
<td>0.003</td>
<td>69.7±14.0</td>
<td>69.4±16.3</td>
<td>0.63</td>
</tr>
<tr>
<td>Mitral A wave, cm/s</td>
<td>76.0±23.4</td>
<td>76.3±23.5</td>
<td>0.95</td>
<td>74.8±24.7</td>
<td>82.1±25.6</td>
<td>0.46</td>
</tr>
<tr>
<td>E/E’</td>
<td>7.1±2.4</td>
<td>6.7±1.5</td>
<td>0.41</td>
<td>8.0±3.1</td>
<td>7.5±3.5</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Data are displayed as mean ± SD. Abbreviation: BNP, B-type natriuretic peptide.
face of stable arterial properties, such as pulse wave velocity or wave reflection. The change in augmentation may be attributable to a shorter ejection period, decreased ventricular contractility, or reduced ability of the ventricle to augment pressure because of decreased preload. Similar preload effects may explain the decrease in AI with no change in pulse wave velocity after administration of nitrates.22

Our study also suggests that it is important to reserve use of intravenous BNP therapy to patients with elevated filling pressures, where a drop in preload is much less likely, and also that the duration of therapy should be limited to that time period when there is significant preload elevation. Use of intravenous BNP in patients with heart failure and preserved ejection fraction should be undertaken cautiously because these patients are prone to more rapid drops in preload than patients with reduced ejection fraction.

This study has clear limitations. Because of the small number of participants, the data should be interpreted as hypothesis generating. However, the fact that each participant served as his or her own control before a standardized physiological perturbation strengthens the conclusions. The study was powered for the primary analysis only, and other significant findings must be interpreted as exploratory rather than definitive. Changes in intracardiac volumes and pressures were not measured; thus, the discussion regarding preload is speculative and based on known effects of BNP as well as results of echocardiographic measures of diastolic function and filling. This study included reasonably healthy older participants, and the data may not be fairly extrapolated to younger or sicker populations. Our participants were white, and the degree to which the data reflect physiology in other races or ethnicities is unknown.

In summary, ventricular performance did not improve after a fall in late systolic pressure augmentation as a result of human recombinant BNP infusion in a group of older participants. There was no evidence that reduced wave reflection improved ventricular relaxation or resulted in an obligatory increase in cardiac output.

REFERENCES


ACKNOWLEDGMENTS

Dr Sweitzer was supported by a grant from the National Institutes of Health (AG01022 K23). This study was also supported by a grant from the General Clinical Research Centers Program of the National Center for Research Resources, National Institutes of Health (M01 RR03186).

DISCLOSURE

Dr Mitchell is the president and CEO of Cardiovascular Engineering, a company that designs and manufactures devices that measure vascular stiffmess. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness. All other authors declared no conflict of interest.