Pulse Pressure and Coronary Atherosclerosis Progression in Postmenopausal Women

Girish V. Nair, David Waters, William Rogers, Glen J. Kowalchuk, Thomas D. Stuckey, David M. Herrington

Abstract—Pulse pressure, an index of large artery stiffness, has been associated with coronary events. However, mechanisms for this association remain unclear. In this study, we examined the relationship between pulse pressure and the progression of coronary atherosclerosis and the effects of hormone replacement therapy (HRT) on pulse pressure in postmenopausal women with angiographically confirmed coronary disease followed for 3.2 years in the Estrogen Replacement in Atherosclerosis (ERA) trial. In the ERA trial, 309 postmenopausal women (mean age 66±7 years) with coronary disease were randomized to estrogen, estrogen plus progestin, or placebo, and followed for 3.2 years. Ten standardized epicardial segments were measured for minimal diameter values at baseline and follow-up using quantitative coronary angiography. For this study, mixed-model analysis of covariance was used to: (1) test the association between pulse pressure and change in mean minimum diameter (MMD) adjusted for baseline MMD and (2) the effect of HRT on follow-up pulse pressure. After adjustment for potential confounders, there was a significant graded increase in progression of coronary stenosis with increasing quartiles of baseline pulse pressure (P test for trend=0.0001). The progression rate in women with the highest quartile of baseline pulse pressure was 5-fold higher than in women in the lowest quartile (P<0.01). In postmenopausal women with coronary disease, increased levels of baseline pulse pressure are associated with subsequent progression of coronary atherosclerosis in postmenopausal women. HRT had no detectable effect on pulse pressure. (Hypertension. 2005;45:53-57.)

Key Words: pulse ■ atherosclerosis ■ women

Pulse pressure, an index of large artery stiffness,1 is a significant predictor of coronary artery disease outcomes, including myocardial infarction2–5 and restenosis after percutaneous coronary intervention.6 However, the mechanisms underlying this association remain to be elucidated. In animal models, increased aortic stiffness is associated with coronary ischemia7 and progression of coronary atherosclerosis.8 In clinical studies, increased pulse pressure (PP) has been associated with atherosclerosis progression in the aorta9,10 and carotid arteries,11–14 but its relationship to coronary atherosclerosis progression in humans remains unknown.

Any association between PP and coronary atherosclerosis progression in women may be confounded by hormonal status. Studies in healthy postmenopausal women suggest hormone replacement therapy (HRT) use may have favorable effects on large artery compliance.15–18 However, these effects may be limited to specific formulations of HRT17,19 or certain subgroups of women.19 Furthermore, aging, established atherosclerosis,20 or concomitant progestin use21 may attenuate some of the favorable effects of estrogen on vasculature. Additional studies are needed to examine the association of PP with coronary atherosclerosis progression in postmenopausal women and assess the impact of HRT use on PP.

In this study, we examined the relationship between PP and the progression of coronary atherosclerosis and the effects of HRT on PP in postmenopausal women with angiographically confirmed coronary disease followed for 3.2 years in the Estrogen Replacement in Atherosclerosis (ERA) trial.22

Methods

Subjects

The design, methods, and primary results of the ERA trial have been published previously.22–24 Briefly, the ERA trial was a 3-arm, randomized, controlled trial of 0.625 mg of conjugated equine estrogen (CEE), 0.625 mg of CEE plus 2.5 mg of medroxyprogesterone acetate (MPA), or placebo in 309 postmenopausal women aged <80 years with angiographically verified coronary disease. Coronary disease was defined as at least 1 stenosis of 30% in any single coronary artery. Participants gave informed consent, and institutional review boards at each participating clinical site approved the study.

Blood Pressure Measurements

Blood pressure was measured in the seated position after a 5-minute rest period by trained and certified staff using standard methods.
Baseline and annual follow-up measurements were based on the average of the second and third readings obtained at each visit. PP was calculated as the difference between the averaged systolic blood pressure (SBP) and diastolic blood pressure (DBP) readings (PP = SBP – DBP). Mean arterial pressure (MAP) was calculated as the sum of one-third the SBP plus two-thirds the DBP (MAP = 1/3 SBP + 2/3 DBP). In the ERA trial, women were excluded if they had an initial SBP >200 mm Hg, DBP >105 mm Hg, or if the mean of the second and third measurements exceeded 170/90 mm Hg.

Outcomes
Coronary angiograms were acquired in an identical standardized fashion at baseline and follow-up. Clinically indicated coronary angiograms obtained within 6 months of the scheduled closeout angiogram were treated as a final angiogram. A previously validated system of cine projectors (SME-2500; Sony) and software (QCAPlus; Sanders Data Systems) were used for review and analysis of the paired films. Reference, minimal, and average luminal diameters were measured using quantitative coronary angiography of 10 standardized epicardial segments. The mean intraoperator difference between blind duplicate measures of minimum diameter with this system is 0.02 mm. Operators performing the analyses were blinded to treatment assignment or the temporal sequence of the films.

Statistical Analysis
Baseline PP was divided into approximate quartiles by 10 mm Hg increments (<50, ≥50 to 60, ≥60 to 70, and ≥70 mm Hg). Analysis of covariance was used to identify baseline variables independently associated (P < 0.05) with PP in a multivariable model. The association between quartiles of PP and change in mean minimum coronary artery diameter was tested using mixed-model analysis of covariance after adjusting for baseline mean minimum diameter (MMD), study treatment, clinic site, location of the arterial segment, duration of follow-up, baseline cardiovascular medications, cardiovascular risk factors, and factors that modify PP independent of baseline diameter, cardiovascular risk factors, and baseline PP. The current study extends earlier studies of men and women. However, there are relatively few nonwhite participants, resulting in larger variances around the point estimates. No clear relationship between change in MMD and PP level was seen in the relatively few women with DM, but a direct relationship was observed in women without DM. Finally, the observed inverse relationship between change in MMD and PP level was not affected by baseline serum creatinine level.

Effects of HRT on PP
At baseline, no overall difference in PP among the 3 treatment arms was observed (placebo 60±14 mm Hg; CEE only 58±14 mm Hg; CEE+MPA 62±15 mm Hg; P = 0.09). During the trial, an increase in mean PP was noted in all 3 treatment arms (P value for time = 0.0008; Figure 2). However, when the effect of treatment on follow-up PP was analyzed, no significant association was found (CEE P = 0.88; CEE+MPA P = 0.80, relative to placebo) after adjusting MAP and baseline PP. Similar results were obtained when the data from the 2 active treatment arms were considered in combination (HRT versus placebo; P = 0.95).

Discussion
In this study of women with angiographically defined coronary disease, increased levels of PP were associated with coronary disease progression during 3.2 years of follow-up, independent of baseline diameter, cardiovascular risk factors, and hemodynamic factors known to influence PP. HRT had no significant effect on PP. The current study extends earlier work suggesting that arterial stiffness may be a cause as well as a consequence of atherosclerosis and may help account for the prospective association between measures of arterial stiffness and clinical coronary heart disease events.

In previous studies have documented an association between arterial stiffness and extent or progression of peripheral arterial disease in animal models of atherosclerosis and in clinical studies of men and women. However, there are relatively few data on the association between indices of arterial stiffness...
and coronary atherosclerosis in humans. In 1 small cross-sectional study that included only 12 women,29 reduced carotid and aortic compliance were associated with severity of coronary disease. A more recent case-control study demonstrated an association between increased arterial stiffness and coronary artery disease in symptomatic men undergoing coronary angiography.30 Because of their designs, a temporal relationship between arterial stiffness and coronary artery disease progression could not be assessed with either study.

Age-related aortic stiffness may be greater in women than in men.31 Large artery distensibility decreases after menopause,32 but small, short-term studies in relatively healthy, postmenopausal women suggest HRT use may attenuate arterial stiffness.15,16 This effect may vary by formulation of HRT and be limited to certain subgroups of women.17,19 In the ERA trial, neither CEE alone nor CEE plus MPA affected on-trial PP. The absence of an effect of HRT on arterial stiffness in the ERA trial versus previous studies may be because women in our study had established atherosclerosis. The presence of established atherosclerosis has been shown to reduce the favorable effects of estrogen on the vasculature.20

In small clinical studies, use of angiotensin-converting enzyme inhibitors (β-blockers), diuretics, and clonidine have been associated with modest reductions in arterial stiffness.33–35 Statin use has also been associated with reduced arterial stiffness independent of reductions in cholesterol in patients with hypercholesterolemia.36 None of these agents are designed to specifically modify arterial composition. This may limit their utility as an effective therapy for arterial stiffness.

In contrast, recent experiments with a novel class of agents, thiazolium derivatives, have demonstrated significant im-
Figure 1. Impact of baseline PP on coronary disease progression. Adjusted for baseline MMD, location of artery segment, length of follow-up, clinic site, imputed measures, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, early events, study treatment, NSAID use, lipid treatment, age, race, cardiovascular disease, risk factors, MAP, heart rate, and height.

Proven in arterial and cardiac compliance associated with reductions in nonenzymatic cross-links between vascular matrix proteins.37,38 In a recent multicenter, randomized, placebo-controlled trial, administration of ALT-711, the newest agent in this class, significantly reduced total arterial compliance and PP independent of MAP in a cohort of elderly men and women.39 Future long-term data on efficacy and safety are needed to evaluate this new class of agents.

This study is not without limitations. Because this was a nonrandomized analysis, the association between PP and disease progression may be confounded by unmeasured factors that influence progression and are differentially distributed across PP groups. In addition, blood pressure was not a primary outcome in the ERA trial; thus, measured blood pressures may not reflect an individual’s usual blood pressure. In this study, we used brachial PP measurements to make inferences about central PP, specifically aortic stiffness. This method has the potential to overestimate true central PP because of pressure amplification and may be less sensitive than central pressure measures as an index of coronary artery disease severity.32 However, in older subjects, this may be less problematic because of increased peripheral resistance and an earlier return of the reflected wave.26 Although we demonstrate an association between increased PP and coronary atherosclerosis progression, it is still unclear whether this portends coronary atheroma vulnerability and subsequent plaque rupture and cardiovascular events. Finally, the women in the ERA trial were primarily white, had established coronary disease, and were participants of a randomized trial; therefore, these data may not be generalizable to all women.

**Perspectives**

These data provide additional insight into the pathogenesis of coronary atherosclerosis and offer additional evidence to suggest that new therapeutic agents designed to treat arterial stiffness may be another effective treatment to forestall the progression of coronary disease. Future physiological studies examining the effects of increased arterial stiffness on coronary atheroma would greatly enhance our understanding of coronary disease progression and acute coronary syndromes and better guide future therapies.

**Acknowledgments**

E.R.A. was supported in part by HL 45488, National Heart, Lung, and Blood Institute, Bethesda, Md, and the Wake Forest University Baptist Medical Center General Research Center grant M01-07122. We are indebted to Bonny P. McClain, MS, for her editorial contributions.

**Table 2. Mean (mean±SE) Changes in MMD According to Baseline PP (mm Hg) Quartile in Selected Subgroups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>PP&lt;50 (mm)</th>
<th>50≤PP&lt;60 (mm)</th>
<th>60≤PP&lt;70 (mm)</th>
<th>PP≥70 (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥66 years</td>
<td>157</td>
<td>0.082±0.065</td>
<td>-0.047±0.055*</td>
<td>-0.072±0.057†</td>
<td>-0.107±0.054‡</td>
</tr>
<tr>
<td>&lt;66 years</td>
<td>151</td>
<td>-0.077±0.043</td>
<td>-0.105±0.040</td>
<td>-0.111±0.043</td>
<td>-0.159±0.046</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>206</td>
<td>-0.063±0.044</td>
<td>-0.125±0.038</td>
<td>-0.170±0.041†</td>
<td>-0.204±0.038‡</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>102</td>
<td>0.032±0.077</td>
<td>-0.071±0.069</td>
<td>-0.080±0.065</td>
<td>0.018±0.069</td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>74</td>
<td>0.109±0.116</td>
<td>-0.079±0.087</td>
<td>-0.111±0.096</td>
<td>-0.074±0.080</td>
</tr>
<tr>
<td>Absent</td>
<td>234</td>
<td>-0.013±0.038</td>
<td>-0.060±0.036</td>
<td>-0.085±0.036</td>
<td>-0.121±0.041†</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1.2 mg/dL</td>
<td>47</td>
<td>0.302±0.188</td>
<td>-0.137±0.115†</td>
<td>-0.110±0.110†</td>
<td>-0.155±0.123*</td>
</tr>
<tr>
<td>&lt;1.2 mg/dL</td>
<td>261</td>
<td>0.009±0.037</td>
<td>-0.067±0.034</td>
<td>-0.109±0.035†</td>
<td>-0.131±0.036‡</td>
</tr>
</tbody>
</table>

*Adjusted for clinic site, location of the arterial segment, age, race, cardiovascular risk factors, baseline lipid lowering, NSAID use, MAP, heart rate, height, and calcium blocker use.

†P<0.05 relative to PP<50 mm Hg; ‡P<0.01 relative to PP<50 mm Hg.

Age, race, and diabetes status were not included in the age, race, or diabetes stratified models, respectively.
References


Pulse Pressure and Coronary Atherosclerosis Progression in Postmenopausal Women
Girish V. Nair, David Waters, William Rogers, Glen J. Kowalchuk, Thomas D. Stuckey and David M. Herrington

Hypertension. 2005;45:53-57; originally published online November 15, 2004;
doi: 10.1161/01.HYP.0000149599.99266.44
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/45/1/53

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/