Pulse Pressure and Coronary Atherosclerosis Progression in Postmenopausal Women

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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

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)24,25 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.23 The mean intraoperator difference between blind duplicate measures of minimal, reference, and average diameters was 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 the intrinsic stiffness of the central aorta and brachiocephalic artery (MAP, heart rate, and height).26,27

To investigate the effects of treatment assignment on PP, follow-up PP was modeled using mixed-model analysis of covariance after adjusting for time, MAP, and baseline PP. In performing these analyses, the effects of unopposed estrogen and estrogen plus MPA were analyzed separately and in combination with respect to placebo. A nominal 2-tailed P value <0.05 was considered to be statistically significant. All analyses were conducted using PC SAS 6.12 software.

Results
Baseline Characteristics
In this study, the mean PP was 60±14 mm Hg. The mean SBP and DBP were 134±17 mm Hg and 74±9 mm Hg, respectively. Seventy-four percent of the women were hypertensive based on criteria from the sixth report of the Joint National Committee on high blood pressure (JNC-VI).28

In separate multivariate models, MAP and hypertension status were most strongly associated with baseline PP (Table 1). However, MAP explained a greater proportion of the variance in PP (partial R²=0.27; model R²=0.44) than did hypertension status (partial R²=0.16; model R²=0.27). Other significant independent predictors of baseline PP included age, diabetes, nonsteroidal anti-inflammatory drug (NSAID) use, and calcium channel blocker use.

Association Between PP and Coronary Disease
At follow-up, a stepwise increase in coronary disease progression was observed with increased levels of baseline PP (P value for trend=0.0001; Figure 1). After adjusting for baseline MMD, treatment assignment, and other covariates, women with higher levels of baseline PP (≥50 mm Hg) had a significantly greater reduction in MMD compared with women in the lowest quartile (P<0.05 for second, third, and fourth quartile versus first quartile). Similar results were obtained after additional adjustment for baseline antihypertensive medications (data not shown). SBP and DBP were weakly (P=0.1) and positively associated and significantly (P=0.007) and inversely associated with progression, respectively. End-of-study PP yielded similar associations with progression as the baseline PP.

To determine whether there was a differential relationship between PP and coronary disease progression among certain subgroups, change in MMD was compared among PP quartiles after stratification by age, race, creatinine levels, and presence of diabetes mellitus (DM; Table 2). There was a graded and negative change in MMD in older and younger women with increased levels of baseline PP. A similar trend was noted in white women. Among nonwhite women, there appeared to be a U-shaped relationship between change in MMD and quartiles of PP. However, there were 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+MAP 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.

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.9–14 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, 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. 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. Large artery distensibility decreases after menopause, but small, short-term studies in relatively healthy, postmenopausal women suggest HRT use may attenuate arterial stiffness. This effect may vary by formulation of HRT and be limited to certain subgroups of women. 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.

In small clinical studies, use of angiotensin-converting enzyme inhibitors (β-blockers), diuretics, and clonidine have been associated with modest reductions in arterial stiffness. Statin use has also been associated with reduced arterial stiffness independent of reductions in cholesterol in patients with hypercholesterolemia. 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-

| TABLE 1. Baseline Characteristics of Participants by Quartile of PP (mm Hg) |
|-----------------|---------------|---------------|---------------|---------------|
| Characteristics | PP<50 (n=73)  | 50=PP<60 (n=79) | 60=PP<70 (n=83) | PP>70 (n=73)  |
| Demographic     |               |               |               |               |
| Age (years)     | 63±7          | 65±8          | 67±7          | 68±6          |
| Race, white     | 51 (70)       | 58 (73)       | 49 (59)       | 48 (66)       |
| Married         | 34 (47)       | 38 (48)       | 37 (45)       | 27 (37)       |
| Education       |               |               |               |               |
| <HS             | 31 (43)       | 31 (39)       | 39 (49)       | 30 (41)       |
| HS graduate/VT  | 27 (37)       | 23 (29)       | 30 (38)       | 29 (40)       |
| At least college| 15 (21)       | 25 (32)       | 11 (14)       | 14 (19)       |
| CHD risk factors|               |               |               |               |
| Hypertension    | 39 (53)       | 46 (58)       | 71 (86)       | 71 (97)       |
| DM              | 11 (15)       | 21 (27)       | 19 (23)       | 23 (32)       |
| Current smoker  | 24 (33)       | 19 (24)       | 14 (17)       | 9 (12)        |
| Alcohol use     | 20 (27)       | 16 (20)       | 15 (18)       | 23 (32)       |
| Waist-hip ratio | 85±9          | 87±9          | 86±8          | 87±10         |
| LDL-C (mg/dL)   | 44±12         | 42±10         | 44±12         | 47±13         |
| HDL-C (mg/dL)   | 146±44        | 130±41        | 128±38        | 146±42        |
| Creatinine (mg/dL) | 0.88±0.23 | 0.86±0.27 | 0.87±0.23 | 0.99±0.29 |
| Medications     |               |               |               |               |
| Aspirin         | 51 (70)       | 54 (68)       | 57 (69)       | 55 (75)       |
| NSAID           | 8 (11)        | 15 (19)       | 21 (29)       | 21 (29)       |
| Lipid lowering  | 23 (32)       | 33 (42)       | 32 (39)       | 25 (34)       |
| ACE inhibitor   | 19 (26)       | 15 (19)       | 16 (19)       | 21 (29)       |
| β-blocker       | 28 (38)       | 37 (47)       | 39 (47)       | 32 (44)       |
| CCB             | 34 (47)       | 42 (53)       | 51 (61)       | 48 (66)       |
| Diuretic        | 20 (27)       | 22 (28)       | 25 (30)       | 29 (40)       |
| Nitrates        | 37 (51)       | 31 (39)       | 32 (39)       | 22 (30)       |
| PP determinants |               |               |               |               |
| Height (cm)     | 159±8         | 161±7         | 161±5         | 159±7         |
| Heart rate (bpm)| 68±9          | 70±13         | 67±10         | 71±11         |
| MAP (mm Hg)     | 86±9          | 92±8          | 95±9          | 102±9         |

ACE indicates angiotensin-converting enzyme; CCB, calcium channel blocker; CHD, coronary heart disease; HS, high school; VT, vocational or technical school.

*P for test of association between PP and the characteristic of interest after adjusting for all other variables in the table.
†Multivariate model of PP adjusted for all variables in the table except hypertension.

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In contrast, recent experiments with a novel class of agents, thiazolium derivatives, have demonstrated significant im-
improvements 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 length of follow-up, clinic site, imputed measures, coronary angioplasty, early events, study treatment, NSAID use, lipid treatment, age, race, cardiovascular disease, risk factors, MAP, heart rate, and height.

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.

Figure 2. Effects of HRT (CEE only and CEE+MPA) on PP. Adjusted for time, MAP, and baseline PP. CEE only=0.625 mg of oral CEE only; CEE+MPA=0.625 mg of oral CEE+2.5 mg of MPA.

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.

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