

# Elevated Pulse Wave Velocity Increases the Odds of Coronary Calcification in Overweight Postmenopausal Women

Lakshmi Venkitachalam, Rachel H. Mackey, Kim Sutton-Tyrrell, Ami S. Patel, Miriam A. Boraz, Laurey R. Simkin-Silverman, and Lewis H. Kuller

**Background:** Aortic stiffness, assessed using carotid–femoral pulse wave velocity (cfPWV), predicts all-cause and cardiovascular mortality. Brachial–ankle pulse wave velocity index (baPVI) is a newer measure of arterial stiffness obtained using an automated system. Our aim is to evaluate the association between both these measures of arterial stiffness and coronary calcification (CAC), in overweight/obese postmenopausal women, without apparent cardiovascular disease.

**Methods:** The CAC was assessed using electron beam tomography in 504 postmenopausal women, aged 52 to 62 years (88.2% white) with mean body mass index (BMI) 30.8 kg/m<sup>2</sup>. The CAC scores were analyzed as CAC >0 and CAC >100 versus CAC = 0, or as ln (CAC + 1).

**Results:** The cfPWV was available in 476 women (mean [SD]: 900 (255) cm/sec) and baPVI was available in 441 women (mean [SD]: 1434 (231) cm/sec. Any CAC (CAC >0) was present in approximately 51% of the

cohort. Both high cfPWV (RR = 1.5, 1.6, and 1.7 for quartiles 2, 3, and 4 v 1) and baPVI (RR = 2.9, 3.7, and 4.0 for quartiles 2, 3, and 4 v 1) were associated with the presence of calcification (CAC >0). The association was attenuated but remained significant only for baPVI after adjusting for age, systolic blood pressure, average waist circumference, BMI, fasting glucose, insulin, lipids, hormone replacement therapy, and smoking status. High odds of severe calcification (CAC >100) was seen with the highest quartile of the cfPWV (RR = 5.3) and baPVI (RR = 7.8), and these associations remained significant in multivariable analysis.

**Conclusions:** Both cfPWV and baPVI are associated with presence and severity of coronary calcification in overweight postmenopausal women. Am J Hypertens 2007;20: 469–475 © 2007 American Journal of Hypertension, Ltd.

**Key Words:** Brachial–ankle pulse wave velocity index, coronary calcification, postmenopausal women.

Chronological aging results in stiffening of the arterial wall (arteriosclerosis), a process aggravated by exposure to traditional risk factors such as elevated blood pressure (BP) and glucose abnormalities. Arterial stiffening also exacerbates plaque development (atherosclerosis) and predicts all-cause and cardiovascular mortality among hypertensives and other high-risk populations.<sup>1–3</sup> Increases in arterial stiffness in response to increased risk factors can be observed in young individuals well in advance of atherosclerotic disease.<sup>4</sup> Thus, measures of arterial stiffness are useful barometers of the health of the vascular system and may allow the early identification of individuals at risk for cardiovascular events.

Diagnosis of coronary artery disease (CAD) continues to pose a major challenge in women. It is well known that symptoms in women are less tightly correlated with the presence of CAD. Obstructive CAD has been documented in 25% to 64% of symptomatic women, a prevalence lower than that in men with similar symptoms.<sup>5</sup> On the other hand, approximately 64% of women who die suddenly of cardiac causes have no previous symptoms.<sup>6</sup> Thus, markers of early vascular disease may be particularly useful to identify, at an early stage, women at highest risk of CAD.

Carotid–femoral pulse wave velocity (cfPWV) is an accepted marker of aortic stiffness and a significant predictor of mortality.<sup>2</sup> Also, an association with coronary artery calcification (CAC) has been shown among end-

Received July 3, 2006. First decision November 9, 2006. Accepted November 12, 2006.

From the Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh (LV, RHM, KS-T, ASP, MAB, LRS-S, LHK), Pittsburgh, Pennsylvania; CDC/Virginia Department of Health (ASP), Richmond, Virginia; and The Center for Marital and Sexual

Health in Beachwood (MAB), Beachwood, Ohio.

This research was funded by National Heart, Lung, and Blood Institute contract R01-HL-66468.

Address correspondence and reprint requests to Dr. Kim Sutton-Tyrrell, 505A Parran Hall, 130 DeSoto Street, Pittsburgh, PA 15261; e-mail: tyrrell@edc.pitt.edu

stage renal disease patients<sup>7</sup> and in a community-based sample.<sup>8</sup> However, this relationship has not been evaluated exclusively in overweight/obese postmenopausal women. More recently, an automated measure of arterial stiffness using the brachial and tibial arteries has become commercially available (form ankle-brachial index [ABI]/pulse wave velocity [PWV]; Colin Co. Ltd., Komaki, Japan). It has been validated against invasive measure of aortic PWV,<sup>9</sup> extensively used for research predominantly in Southeast Asia,<sup>10,11</sup> and has been referred to as the brachial ankle PWV (baPWV). There is, however, little information on what this index truly represents and hence, will be referred to as the brachial ankle pulse wave velocity index (baPVI) in the current article.

The purpose of this study is to evaluate the association between arterial stiffening (assessed by cfPWV and baPVI) and atherosclerosis in the coronary arteries (assessed by CAC) in a population of early postmenopausal women. Our study is unique in having both the well-validated, traditional cfPWV and the newer baPVI; although the former is a powerful predictor of mortality and morbidity, the latter is more automated and thus simpler to perform. This analysis, therefore, allows for the comparison of the association of both these indices with an accepted marker of CAD that may, in turn, help understand the baPVI.

## Methods

### Study Population

The Woman on the Move through Activity and Nutrition (WOMAN) study is a randomized clinical trial comparing intensive lifestyle intervention to health education, the details of which have been previously described.<sup>12</sup> Briefly, 508 postmenopausal women, aged 52 to 62 years and free of cardiovascular disease (CVD) at study entry, who met the following criteria were recruited: average waist circumference  $\geq 80$  cm, LDL-cholesterol between 100 and 160 mg/dL, body mass index (BMI) between 25 and 39.9 kg/m<sup>2</sup>, BP  $\leq 160/95$  mm Hg at initial screening but  $\leq 140/90$  mm Hg at randomization, on or off antihypertensive drug therapy, no history of cancer in past 2 years, diabetes or current use of cholesterol-lowering, diabetes, or weight-loss medication. Participants were excluded if they reported a history of substance abuse, eating, anxiety, or psychotic disorder, clinical depression, uncontrolled depression, or a Beck Depression Inventory score of greater than 20. Informed written consent was obtained from all participants at each visit. The study was approved by the Institutional Review Board of the University of Pittsburgh.

Participants completed standardized questionnaires on medical and drug use history, dietary intake, physical activity, alcohol consumption, recent weight history, and hormonal replacement therapy (HRT) use. Cigarette smoking was reported as currently smoking, ever and never having smoked during one's lifetime. The HRT use

was dichotomized as current and ever used. Three measurements of systolic and diastolic BP, each separated by at least 30 sec, were obtained in the right arm after at least 5 min of rest in the seated position. Means of the second and third measurements were used to derive the reported BP for the examination.

Anthropometric measures such as height, weight, and waist circumference were obtained; participants wore light clothes and no shoes. The BMI was then calculated using these measurements. Total cholesterol, HDL-cholesterol, triglycerides, and plasma glucose were determined by conventional methods from fasting blood samples. The LDL-cholesterol was estimated by the Friedewald equation.<sup>13</sup>

### Subclinical Measures

The cfPWV was measured using the protocol described previously.<sup>14,15</sup> Briefly, two nondirectional transcutaneous Doppler flow probes (model 810-a, 10 MHz; Parks Medical Electronics, Aloha, OR) were positioned at the right common carotid and right femoral arteries and the arterial flow waves from the two sites are simultaneously recorded. The data were scored using software developed by the Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging. For each file, a trained reader selects good waveforms, which are then averaged to create composite waveforms for both the carotid and femoral pulse wave. The software averages the selected waveforms and determines the time from the R-wave of the electrocardiogram (ECG) to the foot of each waveform. The difference in timing between the two waves is the time component of the velocity equation. The distance between the sampling sites (carotid and femoral sites) is measured, manually, above the surface of the body with a metal tape measure and is calculated as: carotid-femoral distance = [(suprasternal-umbilicus) + (umbilicus-femoral)] - (carotid-suprasternal), to adjust for the opposite direction of the blood flow in that arterial branch. Aortic pulse wave velocity is then calculated by dividing this distance traveled by the time differential between the two waveforms. Results from all usable data collection runs ( $n = 3$ ) for each participant are averaged. In our laboratory this measure has been demonstrated to have good reproducibility with an intraclass correlation of 0.72 to 0.83.<sup>14</sup>

The baPVI was obtained using an automated system (form ABI/PWV; Colin Co. Ltd.) and protocol described in previous literature.<sup>9</sup> Briefly, after 10 min of rest in a supine position, occlusion and monitoring cuffs are placed around both arms and ankles, following standardized placement procedures. The cuffs contain a plethysmographic sensor to determine volume pulse waveform and an oscillometric pressure sensor to measure BP. Waveforms for the arm (brachial artery) and ankle (tibial artery) are stored for a sampling time of 10 sec with automatic gain analysis and quality adjustment. The "distance" mea-

sure is calculated using height-based formulas rather than the actual “above the body” distances and also corrects for the opposite direction of blood flow by subtracting the heart-to-brachial distance from the heart-to-tibial distance, as seen in the following equation<sup>9</sup>: in the instrument used, path length from the heart to the brachium (Lb) =  $0.2195 \times$  height of the patient (cm) - 2.0734; path length from the heart to ankle (La) =  $0.8129 \times$  height of the patient (cm) - 12.328. The baPVI is calculated by time-phase analysis, for the right and left sides, using waveforms of the respective brachial and ankle (tibial) arterial sites, from the following equation:  $(La - Lb)/$ time difference between the brachial and ankle waveform. An average of baPVI, from the right and left sides, was used in our analyses.

Ankle-brachial index (ABI) information was also available using this system.

Coronary calcification was assessed using electron beam tomography (EBT) performed with an Imatron C150 scanner (Imatron, San Francisco, CA). We obtained 30 to 40 contiguous, 3-mm thick transverse images from the level of the aortic root to the apex of the heart. Images were obtained during maximal breath-holding by using ECG triggering so that each 100-msec exposure was obtained during the same phase of the cardiac cycle, 60% of the RR interval. Calcium scores were calculated by the method of Agatston et al<sup>16</sup> with a densitometry program available on the Imatron C150 scanner. The reproducibility was extremely high, with an intra-class correlation of 0.99.<sup>17</sup>

All of the subclinical measures—coronary calcification, cfPWV, baPVI, and ABI—were measured at the baseline study visit.

## Statistical Analysis

Between April 2002 and December 2003, 508 overweight (BMI: 25 to 39.9 kg/m<sup>2</sup>) women were enrolled in the study at baseline. For the purpose of our analyses, we included only white and African-American women with CAC data, resulting in a sample size of 504. The CAC scores were highly skewed and log transformed according to the following formula:  $\ln(CAC + 1)$  for use as continuous variables and categorized as “any” (CAC >0, which includes values of CAC above 100) and “advanced” (CAC >100) calcification. The PWV measures were analyzed as both continuous values and categorized as quartiles for analyses. Quartiles of cfPWV and baPVI were defined as follows: cfPWV (cm/sec): Q1 = 471 to 739, Q2 = 742 to 846, Q3 = 846 to 989, Q4 = 992 to 2417; baPVI (cm/sec): Q1 = 939 to 1271, Q2 = 1275 to 1405, Q3 = 1405 to 1570, Q4 = 1571 to 2752.

Association between arterial stiffness and coronary calcification was analyzed separately for cfPWV and baPVI. Correlations between CAC, cfPWV, and baPVI were assessed using Spearman’s method. Differences in the mean  $\ln(CAC + 1)$  scores between quartiles of arterial stiffness measures were analyzed using analysis of covariance

(ANCOVA) and tests of trend were carried out using linear contrasts. Binary logistic regression was used to estimate the odds ratio and its 95% CI for “any” (CAC >0) versus “no” calcification for these quartiles, using lowest quartile as reference. Adjusted estimates were obtained from multivariate models that included risk factors associated with any of the three subclinical measures. We also tested for interactions between these established risk factors and arterial stiffness indices. Similar analysis was carried out for odds of “advanced” (CAC >100) versus “no” calcification, after excluding women with CAC scores in the range of 1 to 99. All analyses were performed using SAS statistical software release 8.2 (SAS Institute Inc., Cary, NC). A *P* value  $\leq .05$  was considered significant.

## Results

Our cohort of postmenopausal women had an average age of 57 years and 89% were white (Table 1). In keeping with the study design, they were overweight with a mean waist circumference of 106 cm. Consistent with this, women had high triglycerides and borderline BP (23.6% were on antihypertensive medications). However, LDL-cholesterol and glucose were within normal limits, probably because women currently using lipid-lowering or antidiabetic medications were excluded from the trial. Despite low rates of current smoking, the majority of these women were former smokers and 60% were currently on HRT.

The CAC, measured using EBT was available in 504 women. The median score was 1.03, with almost 50% of the women having a score of zero (Table 2). Among the 476 women with cfPWV, the mean value was 900 cm/sec, with a range of 471 to 2417 cm/sec. Among the 441 women with baPVI, the mean value was 1434 cm/sec with a range of 939 to 2752 cm/sec. The two measures of arterial stiffness were correlated at a level of 0.39 (*P* < .001). Baseline characteristics of women with missing stiffness information were not significantly different from those in whom the measures were obtained (data not shown). The ABI, available in 446 women, were within the normal range of 0.91 to 1.30 for 99.6% of the cohort.

Both arterial stiffness measures were positively correlated with CAC, although baPVI showed a slightly stronger association (Spearman *r* for continuous untransformed variables: cfPWV = 0.18, baPVI = 0.27, *P* value for both: < .001). When analyzed by quartiles of cfPWV and baPVI, mean CAC ( $\ln(CAC + 1)$ ) increased progressively with each quartile, for both the measures (Fig. 1). This trend remained significant even after adjusting for age, systolic BP, waist circumference, BMI, smoking status, HRT use, ethnicity, glucose, insulin, LDL-cholesterol, HDL-cholesterol, total cholesterol, triglycerides, and antihypertensive medications.

Binary logistic regression analyses were next used to evaluate, in separate models, the odds of any versus no calcification (CAC >0 v CAC = 0) and advanced versus no calcification (CAC >100 v CAC = 0), for quartiles of

**Table 1.** Baseline subclinical measures and cardiovascular risk factors in the WOMAN study

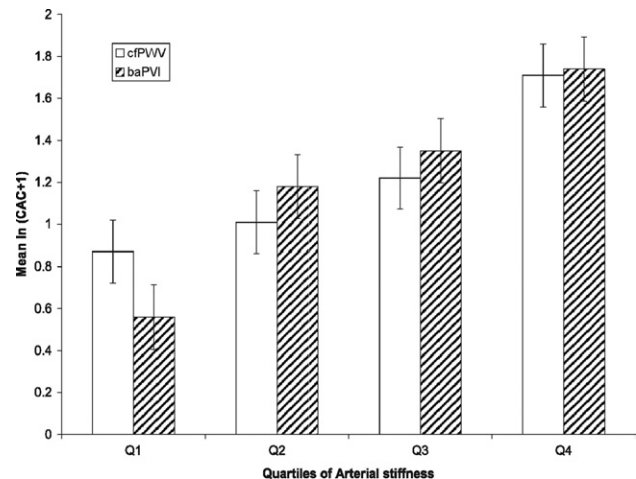
	Total (N = 504)	
	N	%
Race		
African-American	57	11.7
White	448	88.7
Smoking status		
Never	244	48.7
Former	226	45.1
Current	31	6.2
Use of HRT		
Never/former	202	40
Current	303	60
	<b>Mean ± SD*</b>	
Age (y)	57.0 ± 2.9	
Systolic blood pressure (mm Hg)	126 ± 14	
Diastolic blood pressure (mm Hg)	81 ± 9	
Body mass index (kg/m <sup>2</sup> )	30.8 ± 3.8	
Waist circumference (cm)	105.9 ± 11.2	
Total cholesterol (mg/dL)	216.8 ± 27.9	
HDL (mg/dL)	60.2 ± 14.1	
LDL (mg/dL)	128.0 ± 25.2	
Triglycerides (mg/dL)†	125.0 [32.0–580.0]	
Glucose (mg/dL)	95.3 ± 9.3	
Insulin (μmol/IU)	13.6 ± 6.6	

\* SD = standard deviation; SI conversion factors: to convert total cholesterol, HDL, LDL and triglycerides to mmol/L, multiply by 0.0259; to convert glucose to mmol/L, multiply by 0.0555; to convert insulin to pmol/L, multiply by 6.945; † Median and range within parentheses, given because distribution was skewed.

cfPWV and baPVI, using the lowest quartile as reference (Table 3). In the model with any CAC as the outcome, both high cfPWV and high baPVI were associated with higher odds of calcification. After adjustment for ethnicity, BMI, waist circumference, smoking status, HRT use, glucose, insulin, total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, and antihypertensive medications,

**Table 2.** Baseline subclinical measures in the WOMAN study

	N (%)
Coronary calcium score	
0	247 (49.0)
1–10	162 (32.1)
11–100	67 (13.3)
>100	28 (5.6)
	<b>Mean ± SD</b>
Average cfPWV (cm/sec)	901 ± 256
Average baPVI (cm/sec)	1434 ± 232

**FIG. 1.** Mean coronary calcium scores (ln (CAC+1)) by quartiles of arterial stiffness measures; *P* value for trend: carotid–femoral pulse wave velocity = .01, brachial–ankle pulse wave velocity index = .002.

the association remained statistically significant only for baPVI. No significant interactions were observed between these risk factors and the arterial stiffness indices. However, in the model with advanced CAC (CAC > 100) as the outcome, the highest quartile of both cfPWV and baPVI was associated with a five- and seven-fold higher odds ratio (*P* < .05), respectively, after multivariable adjustment. Inclusion of pulse pressure instead of systolic BP did not alter these results.

## Discussion

In our cohort of overweight and obese, but relatively young, postmenopausal women, elevated arterial stiffness measures—carotid–femoral (aortic) pulse wave velocity and baPVI—were associated with presence and severity of coronary calcification, as measured by EBT. This is also the first report that directly compares the standard aortic PWV with the automated baPVI in a predominantly white population. Mean baPVI values were higher than cfPWV with a reasonable correlation between the two measures. The baPVI also showed a stronger association than the standard cfPWV with CAC, which was independent of well-known confounders including age, systolic BP, BMI, lipids, glucose, and even pulse pressure, an important marker of arterial stiffness.

Review of literature for association between CAC and measures of arterial stiffness revealed equivocal results.<sup>18</sup> Elevated PWV, be it carotid–femoral PWV in the elderly<sup>19</sup> and end-stage renal disease patients<sup>7</sup> or baPVI in type 2 diabetics,<sup>10</sup> was associated with high levels of coronary calcification in these population subsets. However, there were also studies, with little or no representation of women, that showed no correlation between CAC and either aortic<sup>20</sup> or baPVI.<sup>21</sup> Arterial stiffness results in the loss of shock-absorbing capacity of blood vessels and increased shear stress. The ensuing vascular damage pro-

**Table 3.** Odds of any (CAC >0) and advanced (CAC >100) coronary calcification by quartiles of arterial stiffness measures

	Carotid-femoral PWV (N = 447)				Brachial-ankle PWV index (N = 442)			
	Any (>0) v no CAC		Advanced (>100) v no CAC		Any (>0) v no CAC		Advanced (>100) v no CAC	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Unadjusted								
Q1	1.00	—	1.00	—	1.00	—	1.00	—
Q2	1.04	0.62–1.73	2.03	0.49–8.43	2.88†	1.64–5.05	1.49	0.29–7.67
Q3	1.81*	1.08–3.02	2.64	0.63–11.04	3.72†	2.12–6.55	4.01*	0.99–16.26
Q4	2.32‡	1.38–3.90	5.18*	1.35–19.86	3.95†	2.24–6.97	7.78†	2.10–28.79
Adjusted for age, systolic BP								
Q1	1.00	—	1.00	—	1.00	—	1.00	—
Q2	0.93	0.55–1.57	1.73	0.40–7.27	2.52†	1.42–4.47	1.32	0.25–6.91
Q3	1.65	0.98–2.78	2.51	0.58–10.63	3.15†	1.77–5.62	3.81	0.93–15.66
Q4	1.91*	1.12–3.27	4.13*	1.03–16.30	2.59†	1.41–4.75	5.26*	1.30–2.38
Adjusted for above+ waist circumference, BMI, smoking status, HRT use, race, glucose, insulin, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and antihypertensive medications								
Q1	1.00	—	1.00	—	1.00	—	1.00	—
Q2	0.78	0.43–1.43	1.79	0.35–9.28	1.94*	1.01–3.70	2.69	0.35–20.91
Q3	1.68	0.94–3.01	2.78	0.62–14.44	2.90†	1.50–5.58	5.32	0.86–32.92
Q4	1.64	0.90–2.98	4.55	0.94–22.11	2.21*	1.11–4.42	7.86*	1.43–43.17

\*  $P \leq .05$ ; †  $P \leq .01$ ; ‡  $P \leq .001$ .

motes atherosclerosis, which may not always be clinically apparent. Interestingly, our cohort, by study design, was free of clinical CVD at the time of entry. Yet, women with higher cfPWV or baPVI had higher odds of calcification, indicating extensive subclinical disease among the subset. Overweight postmenopausal women are a growing segment of the population in America. In a study of unselected patient population,<sup>22</sup> coronary calcification was present in 37% of women aged 50 to 59 years. In contrast, approximately 50% of our women in the same age range had any CAC. The high burden of subclinical disease and the increased risk of coronary calcification with increasing PWV is, therefore, a matter of public health concern.

Carotid–femoral PWV is considered the gold standard for noninvasive approximation of central or aortic PWV and has been shown to be a significant predictor of cardiovascular events, both in older<sup>23,24</sup> and younger adults.<sup>25</sup> The baPVI is less well characterized, but its ease of use has led to increased utilization as an index of arterial stiffness in research, and perhaps even for clinical purposes, in Southeast Asia. Our report highlights its association with CAC, a well-known marker of cardiovascular events and the difference in the strength of association seen between baPVI and cfPWV, with CAC, is interesting. We speculate that cfPWV and baPVI may be differentially influenced by pathology in different arterial segments. Although cfPWV is an accepted marker of aortic stiffness, baPVI, calculated using waveforms recorded at the brachial and tibial arteries, may be influenced by femoral and lower branches of the arterial tree. Although this would also explain the modest correlation of baPVI with cfPWV, differences in the two indices could also be attributed to their varying technique of measurement. Whereas the cfPWV requires skilled use of Doppler probes, the newer index, baPVI, is obtained by plethysmographic sensors in cuffs placed on the limbs. In addition, although the “distance” used to calculate both cfPWV and baPVI is an estimate of the path length traveled by the pulse waveform, the path lengths per se, for baPVI, are calculated using height-based equations<sup>9</sup> rather than the actual “above the body” distances used in cfPWV. We did, however, adjust for body height in our analyses, which did not affect the significance of the association of baPVI and CAC (data not shown).

Given the inclusion of the arteries of the leg in the baPVI, this measure reflects more of the peripheral arterial system than cfPWV, which targets the aorta. Peripheral vascular disease, per se, diagnosed using ankle–arm index (ABI), is strongly indicative of atherosclerosis in other arterial beds, and as such a significant predictor of total and cardiovascular mortality.<sup>26</sup> However, relatively advanced disease is required for an abnormal ABI. Elevated baPVI, on the other hand, may be highly sensitive to vascular changes, explaining the strong association with CAC seen in our cohort with normal ABI values.

These cross-sectional results are in overweight/obese postmenopausal women and therefore, are specific to the

nature of the cohort and cannot establish causality. The prevalence of advanced calcification is low in our cohort of relatively healthy women, which may weaken the relevance of the odds ratio in this category. The pattern of association is, however, similar to that seen with “any” CAC. These results provide information on baseline subclinical disease, and allows for evaluation of the effect of lifestyle intervention.

In conclusion, both the gold standard measure of aortic PWV (cfPWV) and the newer automated arterial stiffness index (baPVI) were significantly associated with both the presence and severity of coronary calcification, among overweight postmenopausal women, even within the narrow range of BMI in this study. The baPVI showed slightly stronger association with presence of CAC, whereas both cfPWV and baPVI remained significantly associated with severity of CAC after adjustment for shared cardiovascular risk factors. The baPVI is easily obtained using an automated system, making it ideal for use in large-scale population studies. Further studies to validate baPVI, by evaluating its relationship to the standard cfPWV, and to quantify any incremental information it provides, are therefore warranted.

## Acknowledgments

We acknowledge the contributions of the staff as well as the 508 dedicated participants of the WOMAN study.

## References

- Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM: Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 2001;38:938–942.
- Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A: Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236–1241.
- Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME: Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler Thromb Vasc Biol* 2001;21:2046–2050.
- Gungor N, Thompson T, Sutton-Tyrrell K, Janosky J, Arslanian S: Early signs of cardiovascular disease in youth with obesity and type 2 diabetes. *Diabetes Care* 2005;28:1219–1221.
- Shaw LJ, Shaw RE, Radford M, Kimmel SE, Hewitt K, Krone R, Anderson H, Klein LW: Sex and ethnic differences in the prevalence of significant and severe coronary artery disease in the ACC–National Cardiovascular Data registry. *Circulation* 2004;110:SIII-800.
- American Heart Association: Heart Disease and Stroke Statistics—2006 Update. Dallas, Texas, American Heart Association, 2006.
- Haydar AA, Covic A, Colhoun H, Rubens M, Goldsmith DJ: Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients. *Kidney Int* 2004;65:1790–1794.
- Kullo IJ, Bielak LF, Turner ST, Sheedy PF II, Peyser PA: Aortic pulse wave velocity is associated with the presence and quantity of coronary artery calcium: a community-based study. *Hypertension* 2006;47:174–179.
- Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y: Validity, reproducibility, and clinical significance of noninvasive brachial–ankle pulse wave velocity measurement. *Hypertens Res* 2002;25:359–364.

10. Tsuchiya M, Suzuki E, Egawa K, Nishio Y, Maegawa H, Morikawa S, Inubushi T, Kashiwagi A: Abnormal peripheral circulation in type 2 diabetic patients with normal ankle-brachial index associates with coronary atherosclerosis, large artery stiffness, and peripheral vascular resistance. *Diabetes Res Clin Pract* 2005;70:253-262.
11. Fukuda D, Yoshiyama M, Shimada K, Yamashita H, Ehara S, Nakamura Y, Kamimori K, Tanaka A, Kawarabayashi T, Yoshikawa J: Relation between aortic stiffness and coronary flow reserve in patients with coronary artery disease. *Heart* 2006;92:759-762.
12. Kuller LH, Kriska AM, Kinzel LS, Simkin-Silverman LR, Sutton-Tyrrell K, Johnson BD, Conroy MB: The Clinical Trial of Women On the Move through Activity and Nutrition (WOMAN) study. *Contemp Clin Trials* (in press).
13. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.
14. Sutton-Tyrrell K, Mackey RH, Holubkov R, Vaitkevicius PV, Spurgeon HA, Lakatta EG: Measurement variation of aortic pulse wave velocity in the elderly. *American Journal of Hypertension* 2001;14:463-468.
15. Mackey RH, Sutton-Tyrrell K, Vaitkevicius PV, Sakkinen PA, Lyles MF, Spurgeon HA, Lakatta EG, Kuller LH: Correlates of aortic stiffness in elderly individuals: a subgroup of the Cardiovascular Health Study. *Am J Hypertens* 2002;15:16-23.
16. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R: Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827-832.
17. Sutton-Tyrrell K, Edmundowicz D, Holubkov R, Kuller L: Coronary and aortic calcification by electron beam computed tomography in older adults. *Circulation* 1998;98(Suppl I):I-249.
18. Mackey RH Jr, Venkitachalam L, Sutton-Tyrrell K: Calcifications, arterial stiffness and atherosclerosis. In: Safar ME, Frohlich ED (eds): *Atherosclerosis, Large Arteries and Cardiovascular Risk Adv Cardiol*. Basel, Switzerland, S. Karger, A.G., 2007;234-244.
19. Mackey RH, Sutton-Tyrrell K, Kuller LH, Naydeck BL, Newman AB: Aortic stiffness is associated with aortic and coronary calcification in older adults [Abstract]. *Circulation* 2001;103:1355.
20. Megnien JL, Simon A, Denarie N, Delpino M, Garipey J, Segond P, Levenson J: Aortic stiffening does not predict coronary and extra-coronary atherosclerosis in asymptomatic men at risk for cardiovascular disease. *Am J Hypertens* 1998;11:293-301.
21. Yufu K, Takahashi N, Anan F, Hara M, Yoshimatsu H, Saikawa T: Brachial arterial stiffness predicts coronary atherosclerosis in patients at risk for cardiovascular diseases. *Jpn Heart J* 2004;45:231-242.
22. Janowitz WR, Agatston AS, Kaplan G, Viamonte M Jr: Differences in prevalence and extent of coronary artery calcium detected by ultrafast computed tomography in asymptomatic men and women. *Am J Cardiol* 1993;72:247-254.
23. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, Pahor M, Bauer D, Newman A, for the Health ABC Study: Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation* 2005;111:3384-3390.
24. Mattace-Raso FUS, van der Cammen TJM, Hofman A, van Popele NM, Bos ML, Schalekamp MADH, Asmar R, Reneman RS, Hoeks APG, Breteler MMB, Witteman JCM: Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam study. *Circulation* 2006;113:657-663.
25. Willum Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J: Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006;113:664-670.
26. McKenna M, Wolfson S, Kuller L: The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis* 1991;87:119-128.