# Large-Artery Stiffness Contributes to the Greater Prevalence of Systolic Hypertension in Elderly Women

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**OBJECTIVES:** To determine whether sex differences in large-artery stiffness contribute to the greater prevalence of systolic hypertension in elderly women than in elderly men.

**DESIGN:** During a single visit arterial stiffness was assessed in the unmedicated state using four parameters.

**PARTICIPANTS:** Three hundred seventy-four women with a mean age ± standard deviation of 72 ± 5 and 296 men aged 71 ± 5 participated.

**SETTING:** Hypertensive patients were recruited from general practice as part of the second Australian National Blood Pressure Study in Melbourne, Australia.

**MEASUREMENTS:** Large-artery stiffness was assessed using multiple methodologies, including aortic arch stiffness (β-index) using M-mode ultrasound and arterial compliance and augmentation index using noninvasive carotid pressure and aortic flow measurements.

**RESULTS:** Women had greater carotid and brachial pulse pressure (PP) than men ($P<.001$), despite higher mean arterial pressure in men. Mean arterial compliance was lower in women (0.20 ± 0.12 vs 0.28 ± 0.16 mL/mmHg, $P<.001$) even after correction for aortic area, and aortic arch stiffness was higher (30 ± 36 vs 23 ± 22; $P<.01$). Consistent with both a stiffer proximal circulation and a shorter distance to reflection sites, women had higher augmentation index (38 ± 11% vs 29 ± 12%, $P<.001$). In multivariate analysis, sex was an independent determinant of all arterial stiffness indices.

**CONCLUSION:** Independently of known confounders, elderly hypertensive women have stiffer large arteries, greater central wave reflection, and higher PP than elderly men. Stiffer large arteries likely contribute to the greater prevalence of systolic hypertension in elderly women and may partly explain the acceleration in postmenopausal cerebrovascular and cardiac complications. **J Am Geriatr Soc 52:368–373, 2004.**

**Key words: aging; arterial wall; hypertension; sex**

Isolated systolic hypertension (ISH) affects 26% of the population aged 55 and older[1] and is a strong predictor of cerebrovascular and cardiac events.[2–5] Large-artery stiffening is a principal determinant of systolic blood pressure (SBP) and pulse pressure (PP)[6–8] and thus provides the underlying mechanism for age-related increase in PP.[9,10] Recently, large-artery stiffness has also been independently associated with stroke,[11] coronary disease severity,[12,13] and cardiovascular outcome.[14,15]

The incidence of cerebrovascular and cardiac events in women at all ages is lower than in men but increases disproportionately in women after menopause.[16–18] The mechanisms underlying postmenopausal loss of cardiovascular protection are unclear, but SBP and PP elevation may contribute. Postmenopausal normotensive and untreated hypertensive women exhibit a greater increase in PP than men over a similar age range, due mainly to a greater rise in SBP.[19–21] Furthermore, elderly women have a greater incidence of ISH than elderly men.[1,21] Together these data suggest that postmenopausal women may experience greater age-related stiffening of the large arteries than similarly aged men.

Previous studies have shown that, during the reproductive years, women have a less stiff arterial system than men, but this difference is no longer evident after menopause.[22,23] There is preliminary evidence that healthy older women may actually have stiffer large arteries than elderly men.[23–26] Previous studies have been small or potentially confounded by factors including age, mean arterial pressure (MAP), and vessel size and have not included the elderly (≥65).[23–26] The current study is large and addresses these issues in an elderly hypertensive population. The main aim was to determine whether sex independently influences large-artery stiffness in an elderly population. It was hypothesized that elderly women would

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0002-8614/04/$15.00

have stiffer large arteries than similarly aged men and that this would contribute to the greater prevalence of ISH in elderly women.

## METHODS

### Recruitment

Subjects were recruited from participants in the second Australian National Blood Pressure Study. This trial used a prospective, randomized, open-label design with blinding of endpoint assessments; subject selection criteria and methodology have been reported in detail previously.[27] In brief, subjects were recruited through general practitioners, and their antihypertensive therapy, if any, was withdrawn for a minimum of 2 weeks before assessment (Table 1). A study nurse saw them three times, at least 1 week apart, to assess eligibility for the trial (aged 65–84; untreated SBP > 160 or diastolic blood pressure (DBP > 90 mmHg; no stroke or myocardial infarction within the past 6 months; serum creatinine < 2.5 mg/dL; and no cardiac failure, dementia, or serious comorbidity). Subjects were only included if their average blood pressure on the second and third visits met the inclusion criteria. Blood lipid and random glucose levels were recorded from patient histories. After ascertaining eligibility, but before randomization, participants recruited in the greater Melbourne area were asked to participate in a substudy on large-artery stiffness. The Royal Australian College of General Practitioners Ethics Review Committee approved the main study and the substudy on arterial stiffness, which were implemented in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

### Resting Blood Pressure

Participants rested quietly, supine, for 10 minutes in a darkened room. Supine brachial blood pressure and heart rate were determined oscillometrically before, during, and after arterial stiffness measurements using an automated monitor (Dinamap 1846 SXP, Critikon, Tampa, FL).

### Arterial Stiffness

Arterial stiffness was measured using a variety of techniques to assess structural and functional aspects of the large arteries. Systemic arterial compliance (SAC) was determined from carotid pressure and aortic volume flow as described previously.[28] One study[29] has shown that carotid artery pressure measured using carotid tonometry by experienced operators shows excellent agreement with invasive aortic waveforms. To obtain an estimate of mechanical properties independent of vessel geometry, a distensibility index (DI) was calculated as SAC normalized to left ventricular outflow tract area.[23] Augmentation index (AI) was defined as the difference between the first and second systolic peaks of the carotid artery pressure waveform (obtained via tonometry as previously described for SAC) expressed as a percentage of PP.[30] AI quantifies the elevation in SBP due to greater wave reflection associated with increased pulse wave velocity. Therefore, AI is increased in association with increased aortic stiffness. Experienced operators recorded all waveforms after systematic exploration established that these were maximal for the individual. From a 60-second recording, 10 representative cardiac cycles were analyzed using custom-written software.

**Table 1. Group Characteristics at Screening Visit**

| Characteristic | Women (n = 374) | Men (n = 296) | *P*-value |
|---|---|---|---|
| | Mean ± SD or % | | |
| Age, years | 72 ± 5 | 71 ± 5 | .007 |
| Height, cm | 157 ± 6 | 171 ± 6 | < .001 |
| Weight, kg | 66 ± 11 | 79 ± 11 | < .001 |
| Body mass index, $kg.m^{-2}$ | 26.6 ± 3.9 | 27.1 ± 3.4 | .10 |
| Waist/hip ratio | 0.84 ± 0.06 | 0.94 ± 0.05 | < .001 |
| Glucose, $mmol.L^{-1}$ | 4.8 ± 1.4 | 5.3 ± 2.3 | < .001 |
| Total cholesterol, $mmol.L^{-1}$ | 5.77 ± 0.97 | 5.29 ± 0.96 | < .001 |
| HDL-C $mmol.L^{-1}$ | 1.53 ± 0.45 | 1.21 ± 0.48 | < .001 |
| Total cholesterol/HDL-C ratio | 4.1 ± 1.9 | 4.7 ± 1.5 | < .001 |
| Brachial systolic blood pressure, mmHg | 168 ± 12 | 167 ± 12 | .50 |
| Brachial diastolic blood pressure, mmHg | 88 ± 8 | 90 ± 8 | < .001 |
| Brachial mean arterial pressure, mmHg | 115 ± 7 | 116 ± 7 | .007 |
| Brachial pulse pressure, mmHg | 80 ± 15 | 77 ± 15 | .01 |
| Previous treatment for hypertension, % | 64 | 58 | .15 |
| History of diabetes mellitus, % | 3.2 | 10.5 | < .001 |
| History of myocardial infarction, % | 1.6 | 4.1 | .04 |
| History of coronary artery bypass grafts, % | 0.5 | 2.7 | .02 |
| Ex smokers, % | 32 | 65 | < .001 |
| Frequency of alcohol consumption, % (don't drink, < 2 per d/wk, > 2 per d/wk) | 27, 38, 33 | 9, 35, 55 | < .001 |
| Amount of alcohol consumed, % (0, 1–2 drinks per session, > 2 drinks per session) | 27, 62, 11 | 11, 55, 34 | < .001 |

*Note:* All blood pressures are screening pressures.
HDL-C = high-density lipoprotein cholesterol; SD = standard deviation.

Aortic arch stiffness was measured using the beta index (β-index).[9,31] Briefly, transverse aortic measurements were made from the suprasternal notch as previously described.[9,31] SBP and DBP (mean of three readings) used in this analysis were recorded at the brachial artery using sphygmomanometry immediately after completion of the suprasternal view while the subjects were still recumbent (Dinamap 1846 SXP). β-index was computed as (ln SBP – ln DBP) × $D_d/(D_s - D_d)$ where $D_d$ and $D_s$ are aortic arch diameters in diastole and systole. A person unaware of the hypothesis being tested performed all analyses.

### Statistical Analysis

Data are reported as mean ± standard deviation. Unpaired, two-tailed Student *t* tests and chi-square analyses were used for sex comparisons. β-index, the distribution of which was skewed, was compared using the Mann-Whitney *U* test. Multiple regression was performed to assess determinants of SAC, 1/β-index, and AI. These analyses incorporated the following independent variables: sex, age, MAP, weight, height, heart rate, total cholesterol, high-density lipoprotein cholesterol (HDL-C), blood glucose, smoking status, history of myocardial infarction, stroke, diabetes mellitus, claudication, and coronary artery bypass grafts. It should be noted that adjustment for SBP or DBP gave similar results to adjustment for MAP in all analyses. Statistical significance was taken at the 5% level. Analysis was performed using SPSS for Windows version 10.0.7 (SPSS Inc., Chicago, IL).

## RESULTS

Of the 1,303 patients included in the substudy, 374 women and 296 men, aged 65–84 (women mean age = 72 ± 5, men = 71 ± 5) had all three increments of arterial stiffness.

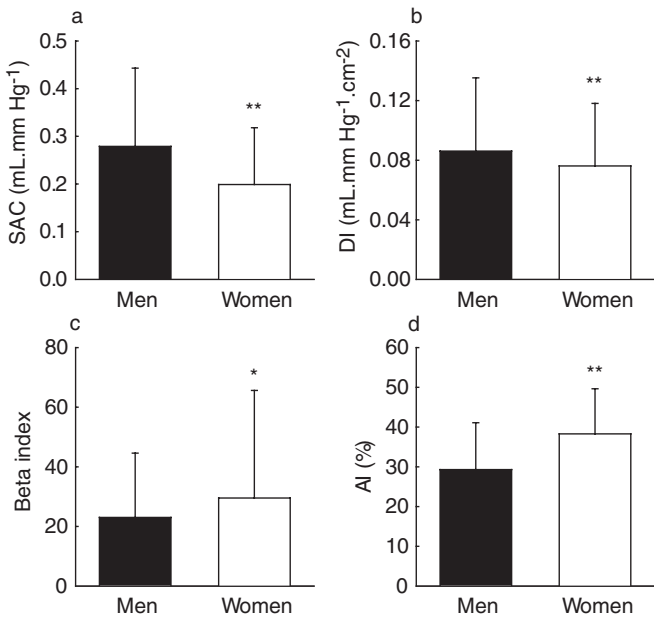


**Figure 1.** Arterial stiffness indices for men (solid bars) and women (open bars). (a) Systemic arterial compliance (SAC), (b) distensibility index (DI), (c) β-index, and (d) carotid augmentation index (AI). Bars are mean ± standard deviation. *$P < .01$; **$P < .001$ women versus men.

lower DBP and MAP than men at screening (Table 1) and during arterial stiffness measurements. At the time of all measurements, subjects had not received antihypertensive medication for at least 3 weeks. A similar percentage of men and women had previously been treated for hypertension (Table 1). All reported sex differences were present in previously treated and never-treated patients.

Using a definition for ISH of SBP of 160 or greater and DBP of less than 90 mmHg, a greater proportion of women had isolated systolic hypertension (49% vs 41%; $P = .001$) despite higher MAP in men (Table 1). On average, men had a higher waist-hip ratio and were heavier and taller than women, but body mass index was not different between the sexes (Table 1). Men also had higher random plasma glucose and lower total cholesterol and HDL-C levels (Table 1).

### Arterial Stiffness

Women had lower SAC than men, indicating lower functional compliance (0.20 ± 0.12 vs 0.28 ± 0.16 mL/mmHg, $P < .001$; Figure 1a). Such differences were independent of variation in vessel geometry, because DI was also lower in women (Figure 1b). Heart rate ((HR) men 67 ± 11; women 70 ± 9 minutes$^{-1}$, $P = .001$) and carotid PP (men 76 ± 29; women 83 ± 26 mmHg, $P < .001$), measured during assessment of large-artery mechanical properties, were higher in women. In multivariate analysis, sex was a determinant of SAC and DI, independent of conventional risk factors and cardiovascular disease history (Table 2). The other major significant determinants of SAC and DI were MAP and age (Table 2).

β-index was higher in women than men (30 ± 36 vs 23 ± 22; $P < .01$, Figure 1c). In multivariate analysis, sex was an independent determinant of β-index, as were MAP and age (Table 2).

AI was also higher in women (38 ± 11% vs 29 ± 12%, $P < .001$, Figure 1d), indicating greater central wave reflection. In multivariate analysis, sex, age, height, HR and MAP were all important determinants of AI (Table 2).

The slope of the relationship between all stiffness indices and age was similar in men and women, but the intercepts were different and consistent with higher stiffness in women.

### Previous History, Medication, and Lifestyle Factors

Hormone replacement therapy (HRT) was taken by 9.6% of female participants. Of these, one-third were taking combined estrogen and progesterone therapy, and two-thirds were on estrogen alone. Eleven percent of men and 15% of women were on cholesterol-lowering medication ($P = .07$). Sex differences in arterial stiffness persisted if patients taking HRT or cholesterol-lowering therapy were dropped from the analysis.

Less than 10% of the population had a previous history of cardiovascular disease. Of these, more men had a history of diabetes mellitus, myocardial infarction, and coronary bypass surgery. There was no difference in the proportion of men and women with a history of claudication, stroke, angina pectoris, or transient ischemic attack. Sex differences in arterial stiffness persisted if patients with a history of any of these conditions were dropped from the analysis.

**Table 2. Determinants of Arterial Stiffness (N = 670)**

| Variable | Predictor | $r^2$ | Partial *r* | *P*-value |
|---|---|---|---|---|
| Systemic Arterial Compliance | | 0.325 | | <.001 |
| | MAP | | −0.47 | <.001 |
| | Male Sex | | 0.14 | <.001 |
| | Age | | −0.14 | .001 |
| | Weight | | 0.11 | .004 |
| | DM | | 0.11 | .008 |
| Distensibility Index | | 0.300 | | <.001 |
| | MAP | | −0.51 | <.001 |
| | Age | | −0.17 | .001 |
| | DM | | 0.11 | .008 |
| | Male Sex | | 0.08 | .04 |
| Beta Index | | 0.088 | | <.001 |
| | Age | | 0.17 | <.001 |
| | MAP | | 0.17 | <.001 |
| | Male Sex | | 0.12 | .003 |
| Augmentation Index | | 0.340 | | <.001 |
| | Heart rate | | −0.40 | <.001 |
| | MAP | | 0.26 | <.001 |
| | Male Sex | | 0.23 | <.001 |
| | Height | | −0.13 | .001 |
| | Age | | 0.12 | .002 |

*Note:* All multivariate analyses incorporated sex, age, mean arterial pressure (MAP), weight, height, heart rate, total cholesterol, high-density lipoprotein cholesterol, blood glucose, smoking status, and history of myocardial infarction, stroke, diabetes mellitus (DM), claudication, and coronary artery bypass surgery.
r = Correlation coefficient.
$r^2$ = Coefficient of determination.

The percentage of current smokers was low for both sexes (5–6%), but more men than women were ex-smokers (Table 1). Frequency of alcohol consumption and amount of alcohol consumed was greater for men ($P<.001$; Table 1). Physical activity was not assessed, but resting HRs (men = $67 \pm 11$; women = $70 \pm 9$ minutes$^{-1}$) were consistent with known sex differences and not likely to relate to differences in activity between the sexes. The above factors were entered in multivariate analysis examining the determinants of large-artery stiffness and could not explain the observed sex differences.

## DISCUSSION

In a large cohort of elderly, hypertensive patients, women had a stiffer proximal circulation, greater central wave reflection, and higher carotid and brachial PPs than men. These differences occurred despite higher MAP in men and were independent of differences in aortic dimensions. Men were slightly younger than women (1 year), and although age was a determinant of arterial stiffness, the effects of sex were independent of age.

Furthermore, clinical variables; previous history; and lifestyle factors, including diabetes mellitus, myocardial infarction, coronary artery bypass grafts, smoking, alcohol consumption, blood glucose, HDL-C levels, and lipid-lowering therapy, were all less favorable for men and therefore not accountable for the observed differences. There was also no difference in the percentage of men and women previously treated for hypertension. Furthermore, all reported sex differences were present in previously treated and never-treated patients. Together these data suggest that elderly hypertensive women have inherently stiffer large arteries than similarly aged men and that this stiffening contributes to higher PP.[19,20] Large-artery stiffening thus likely explains the greater prevalence of ISH in women in the general elderly population.[1,21]

Previous studies have reported lower arterial stiffness in young premenopausal women than in men,[22,23] but it has been shown in relatively small studies that large-artery stiffness is higher in normotensive postmenopausal women.[23,25,26] A mixed population of normotensive and hypertensive pre- and postmenopausal women with a mean age of 53 was also shown to have stiffer large vessels than men.[24] The current study builds on this previous work to specifically examine sex differences in large-artery stiffness in a large, elderly hypertensive population for the first time. Particular care was taken to control for potential confounding factors evident in some of the previous studies in this area. First, higher MAP would be expected to passively increase arterial stiffness, but despite MAP being slightly higher in men, women had stiffer large arteries. Second, DI is independent of geometry and was lower in women. Thus, consistently using a variety of independent techniques, these data indicate that elderly hypertensive women have intrinsically stiffer large arteries than men. Taken together with previous studies, which have collectively encompassed the adult age range below that investigated in the current study,[22–26] women have a greater age-related increase in large-artery stiffness than men.

Large-artery stiffness, distance to the major reflection sites, and HR determine AI.[32] The greater carotid AI in women than in men is a consistent finding across the adult age range and relates partly to a shorter distance to reflection sites associated with shorter stature in women.[32] HR was also slightly higher in women, which would be expected to reduce diastolic duration and contribute to enhanced SBP augmentation.[32] Although height and HR were significant determinants of AI, sex was related independently and likely incorporates a contribution from the higher arterial stiffness observed in women. A recent subgroup analysis of the current cohort, in which women, height-matched to men, had stiffer large arteries and earlier central pressure wave reflection, supports this contention.[33]

### Clinical Relevance

Greater age-related large-artery stiffening in women may contribute to loss of cerebral and cardioprotection postmenopause. Stroke is a leading cause of death and disability for older women, with SBP a major primary and secondary risk factor.[34,35] The current data suggest that large-artery stiffening in women may contribute to an accelerated age-related increase in stroke incidence in older than younger women.[17,18] With regard to cardiac disease, the most likely mechanism associating large-artery stiffening with poor outcome involves increased cardiac work due to SBP elevation and reduced subendocardial perfusion, secondary to lower SBP.[36,37] Furthermore, PP elevation in women would be expected to underlie greater age-related increase in left ventricular mass.[38–40] Such mechanisms may contribute to the greater age-related increase in postinfarct mortality[41–43] and the incidence of congestive heart failure in elderly women.[44,45]

### Study Limitations

Studies were distributed throughout the workday, with 56% of studies in women (55% in men, $P$ = ns) performed between 9 a.m. and 1 p.m. There was no sex disparity in the distribution of studies throughout the workday if analyzed as morning/afternoon or in hourly intervals. Blood samples were random (not fasting), but there were no systematic differences between the sexes in the time of day samples were taken.

Neither diet nor physical activity was assessed, but given that this was a large sample in an elderly population, it is unlikely that physical activity was significantly different between the sexes. Resting HRs were consistent with a normally active lifestyle, and the slight sex difference is consistent with the literature and not likely to be related to differences in activity between the sexes.

Eleven percent of men and 15% of women were on cholesterol-lowering medication ($P$ = .07). Because more women were taking lipid-lowering therapy, this is not likely to be a confounding factor. Sex differences in arterial stiffness persisted if these patients were dropped from the analysis. Of the female participants, 9.6% were taking HRT, but results were unaffected if these patients were removed from the analysis.

The low prevalence of patients with diabetes mellitus relates to the fact that many general practitioners were not comfortable including their diabetic patients in a trial that included subsequent randomization to a diuretic.

## CONCLUSION

In this large cohort of elderly hypertensive patients, arterial stiffness was higher and pressure wave reflection greater in women than men. These sex differences contributed to higher brachial and carotid PP in women, despite lower mean pressure. Therefore, stiffer large arteries contribute to the greater prevalence of ISH in women and may further explain the acceleration in cerebrovascular and cardiovascular complication rate, which occurs postmenopause.

## ACKNOWLEDGMENTS

We are grateful to the participating patients and to the many cooperating general practitioners, whose names may be found at http://www.health.adelaide.edu.au/ANBP2.

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