Hypertension Research (2014) 37, 1021–1027

www.nature.com/hr

ORIGINAL ARTICLE

Gender-specific contribution of aortic augmentation index to variations in left ventricular mass index in a community sample of African ancestry

Moekanyi Jeffrey Sibiya[1,3], Gavin Robert Norton[1,3], Bryan Hodson[1], Michelle Redelinghuys[1], Muzi Joseph Maseko[1], Olebogeng Harold Isaia Majane[1], Elena Libhaber[2] and Angela Jill Woodiwiss[1,3]

Although indices of aortic augmentation derived from radial applanation tonometry are independently associated with adverse cardiovascular effects, whether these relationships are influenced by gender is uncertain. We compared the brachial blood pressure-independent contribution of augmentation index (AIx) to variations in left ventricular mass index (LVMI) in a community sample of 808 participants, 283 of whom were men. Aortic haemodynamics were determined using radial applanation tonometry and SphygmoCor software and LVMI from echocardiography. In men, both AIx derived from aortic augmentation pressure/central aortic pulse pressure (AP/PPc; partial $r = 0.17$, β-coefficient ± s.e.m. $= 0.55 \pm 0.20$, $P < 0.01$) and AIx derived from the second peak/first peak (P_2/P_1) of the aortic pulse wave (partial $r = 0.21$, β-coefficient ± s.e.m. $= 0.42 \pm 0.12$, $P < 0.0005$) were associated with LVM indexed to body surface area (LVMI–BSA). In contrast, in women, neither AIx derived from AP/PPc (partial $r = -0.08$, β-coefficient ± s.e.m. $= -0.20 \pm 0.11$, $P = 0.08$) nor AIx derived from P_2/P_1 (partial $r = -0.06$, β-coefficient ± s.e.m. $= -0.07 \pm 0.05$, $P = 0.17$) were associated with LVMI–BSA. Both the strength of the correlations ($P < 0.001$ and $P < 0.0005$ with *z*-statistics) and the slope of the AIx–LVMI relationships ($P = 0.001$ and $P < 0.0005$) were greater in men as compared with women. The lack of relationship between AIx and LVMI was noted in both premenopausal ($n = 285$; AP/PPc *vs.* LVMI–BSA, partial $r = 0.01$, $P = 0.95$, P_2/P_1 *vs.* LVMI–BSA, partial $r = 0.02$, $P = 0.77$), and postmenopausal ($n = 240$; AP/PPc *vs.* LVMI–BSA, partial $r = -0.06$, $P = 0.37$, P_2/P_1 *vs.* LVMI–BSA, partial $r = -0.03$, $P = 0.64$) women. Similar differences were noted in the relationships between AIx and LVM indexed to height$^{2.7}$ in men and women. In conclusion, radial applanation tonometry-derived AIx may account for less of the variation in end-organ changes in women as compared with men.
Hypertension Research (2014) **37,** 1021–1027; doi:10.1038/hr.2014.113; published online 10 July 2014

Keywords: central aortic augmented index; gender; left ventricular mass index

INTRODUCTION

Although pulse pressure (PP) measured at the brachial artery is closely correlated with central PP (PPc), PPc may be considerably lower than in brachial arteries.[1,2] The factors that determine aortic PP differ markedly from those that determine brachial PP. In this regard, aortic PP is augmented by changes in aortic reservoir function, the timing or magnitude of both the forward and reflected waves and left ventricular systolic function.[1–5] Several studies have demonstrated that indices of aortic pressure augmentation predict cardiovascular events,[6–12] or are associated with end-organ damage independent of or better than brachial blood pressure (BP).[13–16] As indices of aortic pressure augmentation may be derived from simple and highly reproducible tonometric assessments of the radial artery, these indices are attractive additions to routine risk prediction. However, some studies,[12,17,18] including the Framingham Heart Study,[17] have failed to show similar relations between indices of aortic augmentation and cardiovascular outcomes. The factors that determine whether indices of aortic pressure augmentation predict cardiovascular damage therefore require identification.

The impact of gender on aortic augmentation index (AIx; augmentation pressure/aortic PP), is well-recognised. In this regard, women may have a higher AIx than men,[5,19] but these differences may be attributed to factors unrelated to aortic wave reflection.[5] Hence, the impact of AIx on cardiovascular damage in women may not be as strong as that in men. Indeed, although AIx predicts outcomes in men, similar relationships may be diminished in women.[10]

[1]Cardiovascular Pathophysiology and Genomics Research Unit, Faculty of Health Sciences, School of Physiology, University of the Witwatersrand Medical School, Johannesburg, South Africa and [2]Faculty of Health Sciences, The School of Medicine, University of the Witwatersrand, Johannesburg, South Africa
[3]These authors contributed equally to this work.
Correspondence: Professor AJ Woodiwiss, Cardiovascular Pathophysiology and Genomics Research Unit, Faculty of Health Sciences, School of Physiology, University of the Witwatersrand Medical School, 7 York Road, Johannesburg 2193, South Africa.
E-mail: angela.woodiwiss@wits.ac.za
Received 20 February 2014; revised 2 May 2014; accepted 31 May 2014; published online 10 July 2014

Nevertheless, in that study,[10] unadjusted relationships between AIx and end-organ changes were no different in women as compared with men. However, multivariate adjusted relationships between AIx and end-organ changes were not reported on.[10] To clarify whether gender influences relationships between AIx and cardiovascular end-organ changes, we therefore aimed to compare the association between AIx and left ventricular mass index (LVMI) in men and women in a large, community-based sample. In this regard, LVMI and the regression thereof with antihypertensive therapy are well-recognised independent predictors of cardiovascular outcomes.[20–27]

METHODS

Study group

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The present study design has previously been described.[28–30] Briefly, 808 participants from randomly recruited families of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years from the South West Township of Johannesburg, South Africa, and with central haemodynamic measurements and high-quality echocardiograms were studied.

Clinical, demographic and anthropometric measurements

A standardized questionnaire was administered to obtain demographic and clinical data.[28–30] Height and weight were measured using standard approaches and participants were identified as being overweight if their body mass index was $\geqslant 25\,kg\,m^{-2}$ and obese if their body mass index was $\geqslant 30\,kg\,m^{-2}$. High-quality BP measurements were obtained by a trained nurse-technician using a standard mercury sphygmomanometer.[20] Korotkov phases I and V were employed to identify systolic and diastolic BP, respectively, and care was taken to avoid auscultatory gaps. Hypertension was defined as a mean systolic/diastolic BP $\geqslant$ 140/90 mm Hg or the use of antihypertensive medication. Laboratory blood tests of renal function, liver function, blood glucose, hematological parameters and percentage glycated hemoglobin (HbA_{1C}) were performed. Diabetes mellitus (DM) or abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an HbA_{1C} value greater than 6.1%. Menopause was confirmed with measurements of follicle-stimulating hormone concentrations.

Pulse wave analysis

Central aortic systolic BP (SBPc), PPc and AIx were estimated using techniques previously described.[30,31] Briefly, after participants had rested for 15 min in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry during an 8-s period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Houston, TX, USA) interfaced with a computer employing SphygmoCor, version 6.21 software (AtCor Medical Pty, West Ryde, New South Wales, Australia). The pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. The peripheral pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphymoCor software. Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. All measurements were made by a single experienced trained technician unaware of the clinical history of the participants and with a low degree of intraobserver variability and a high degree of reproducibility.[30,31] Central aortic PP was determined as the difference between SBPc and diastolic BP. Augmented pressure (AP) was determined using SphygmoCor software and identified as the difference between PPc and the first systolic shoulder of the aortic pulse wave. Aortic AIx was determined as AP/aortic PP (AP/PPc) expressed as a percentage. To avoid obtaining negative aortic AIx values in young participants, AIx was also determined as the pressure at the second systolic peak of the aortic pulse wave/the pressure at the first systolic peak of the aortic pulse wave (P_2/P_1) expressed as a percentage.[32]

Echocardiography

Left ventricular end diastolic internal diameter and septal (anterior wall) and posterior wall thickness were determined from transthoracic two-dimensional targeted M-mode echocardiographic images obtained in the parasternal long axis as previously described.[28,29,31] Variables were analyzed according to the American Society of Echocardiography convention.[33] All measurements were recorded and analyzed off-line by experienced investigators (CDL and AJW) who were unaware of the clinical data of the participants and whom had a low degree of inter and intraobserver variability.[28,29,31] Only M-mode images of acceptable quality were analyzed. In this regard, acceptable quality was considered to exist when appropriate visualization of both the right and the left septal surfaces occurred and where the endocardial surface of the septal and posterior wall were clearly visible when imaging at the optimal angle of incidence (perpendicular to the posterior wall) and close to the mitral leaflets. Left ventricular mass (LVM) was determined using a standard formula[34] and indexed (LVMI) to height$^{2.7}$ (LVMI-ht$^{2.7}$) and to body surface area (LVMI–BSA). Left ventricular relative wall thickness was defined as (LV anterior + posterior wall thickness at end diastole)/LV end diastolic diameter. LVH was identified as an LVMI–BSA $> 95\,g\,m^{-2}$ for women and $> 115\,g\,m^{-2}$ for men. Concentric LV remodeling was identified as a relative wall thickness $\geqslant 0.42$, and eccentric LVH as a relative wall thickness < 0.42 with an increased LVMI–BSA.

Statistical analysis

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute, Cary, NC, USA) was employed. To determine relationships between PPc or AIx and LVMI, multivariate linear regression analysis was performed. To determine relationships between AIx and concentric LV remodeling, LVH or eccentric LVH in sex-specific groups, multivariate logistic regression analysis was performed. In multivariate models, adjustments were made for the impact of brachial BP (PP, SBP or mean arterial pressure (MAP)), age, body weight, body height (for LVMI–BSA), the presence of diabetes mellitus or an $HbA_{1C} > 6.1\%$, treatment for hypertension, regular tobacco use and regular alcohol intake. To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). To ensure that relationships occurred independent of the use of antihypertensive therapy, sensitivity analysis was conducted in participants not receiving antihypertensive therapy. Regression coefficients were compared with *z*-statistics.

RESULTS

Characteristics of the participants

The clinical and demographic characteristics of women and men are shown in Table 1. Only 1.9% of participants had a history of cardiovascular disease. Importantly, 45.2% of participants with hypertension were not receiving therapy. Moreover, 35.4% of all participants and 28.0% of participants not receiving antihypertensive therapy had uncontrolled hypertension. Participants (19.1%) had concentric LV remodeling and 17.3% had LVH (7.1% concentric and 10.2% eccentric LVH). More women than men had concentric LV remodeling, but a similar proportion had LVH, with no differences noted in the proportion with concentric and eccentric LVH (Table 1). Women had a higher AIx than men, but PPc was similar in men and women (Table 1).

Relationships between aortic BP and LVMI independent of brachial BP in gender-specific groups

PPc was related to LVMI independent of mean arterial pressure in both men and women (Table 2, Figure 1). However, the strength of the relations (partial *r*) was greater in men than in women (Table 2).

Table 1 Characteristics of the study sample

	Men (n = 283)	*Women (n = 525)*	P-*value*
Age (years)	43.0 ± 19.0	45.3 ± 17.5	= 0.09
Body mass index (kg m^{-2})	25.9 ± 16.1	32.6 ± 13.6	< 0.0001
Body weight (kg)	71.9 ± 17.6	80.2 ± 29.2	< 0.0001
Body height (m)	168.5 ± 8.7	157.4 ± 7.1	< 0.0001
% Obese	17.7	56.6	< 0.0001
Regular tobacco (% subjects)	33.6	4.8	< 0.0001
Regular alcohol (% subjects)	33.2	12.4	< 0.0001
% With DM or HbA_{1C} > 6.1%	21.2	28.4	< 0.05
% Women postmenopausal	—	45.7	—
% Hypertensive	40.3	45.3	= 0.17
% Treated for hypertension	15.6	30.7	< 0.0001
% Hypertensives controlled to target BP[a]	28.1	39.1	< 0.05
% of all with uncontrolled BP[b]	38.9	33.5	= 0.14
Pulse rate (beats min^{-1})	62 ± 12	68 ± 11	< 0.0001
Conventional SBP/DBP (mm Hg)	131 ± 22/85 ± 13	128 ± 23/83 ± 13	= 0.07/< 0.05
Conventional pulse pressure (mm Hg)	45.9 ± 18.0	44.5 ± 15.3	= 0.26
Central SBP (mm Hg)	121 ± 22	120 ± 23	= 0.29
Central pulse pressure (PPc; mm Hg)	35.9 ± 17.1	35.7 ± 14.1	= 0.90
Aortic augmentation index (AP/PPc)[c] (%)	23.9 ± 12.8	28.8 ± 12.5	< 0.0001
Aortic augmentation index (P_2/P_1)[d] (%)	135 ± 22	145 ± 25	< 0.0001
Left ventricular mass index (g m$^{-2.7}$)	40.4 ± 14.8	42.3 ± 15.1	= 0.07
Left ventricular mass index (g m^{-2})	82.8 ± 34.4	72.1 ± 27.7	< 0.0001
Left ventricular relative wall thickness	0.38 ± 0.08	0.39 ± 0.08	< 0.05
Concentric LV remodeling (%)	14.8	21.3	< 0.05
Concentric LV hypertrophy (%)	7.4	6.9	= 0.77
Eccentric LV hypertrophy (%)	8.5	11.1	= 0.25

Abbreviations: AP, aortic augmentation pressure; BP, blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA_{1C}, glycosylated hemoglobin; Hg, hemoglobin; LV, left ventricular; PPc, central pulse pressure; SBP, systolic blood pressure.
Data are expressed as mean ± s.d. or proportions. Data were compared with χ^2-analysis or a Student's unpaired *t*-test.
[a]indicates conventional SBP/DBP < 140/90 mm Hg.
[b]indicates conventional SBP/DBP ⩾ 140/90 mm Hg.
[c](Augmentation pressure/aortic pulse pressure) × 100.
[d](Pressure at the second systolic peak of the aortic pulse wave/pressure at the first systolic peak of the aortic pulse wave) × 100.

Table 2 Brachial blood pressure-independent relations between central PPc and LVM index in men and women from a community sample

	Men			*Women*		
Adjustments	n	*Partial* r* *(95% CI)*	P-*value*	n	*Partial* r* *(95% CI)*	P-*value*
PPc vs. LVM indexed to body surface area						
+ Brachial SBP[a]	283	0.25 (0.14 to 0.36)	< 0.0001	525	0.05* (−0.03 to 0.14)	= 0.23
+ Brachial PP[a]	283	0.14 (0.02 to 0.25)	< 0.05	525	0.02 (−0.07 to 0.10)	= 0.71
+ Brachial MAP[a]	283	0.27 (0.16 to 0.38)	< 0.0001	525	0.13* (0.04 to 0.21)	< 0.005
PPc vs. LVM indexed to height$^{2.7}$						
+ Brachial SBP[a]	283	0.27 (0.16 to 0.38)	< 0.0001	525	0.06* (−0.03 to 0.14)	= 0.18
+ Brachial PP[a]	283	0.18 (0.06 to 0.29)	< 0.005	525	0.02* (−0.07 to 0.11)	= 0.65
+ Brachial MAP[a]	283	0.29 (0.18 to 0.39)	< 0.0001	525	0.11* (0.02 to 0.19)	< 0.05

Abbreviations: CI, confidence interval; LVM, left ventricular mass; MAP, mean arterial pressure; OR, odds ratio; PP, pulse pressure; PPc, central pulse pressure; SBP, systolic blood pressure.
*$P < 0.05$ for comparison of *r* values between men and women using *z*-statistics.
[a]Adjustments are for age, body weight, height (for LVM indexed for BSA), the presence of diabetes mellitus or an HbA1c > 6.1%, pulse rate, treatment for hypertension (in all participants), regular tobacco use and regular alcohol intake and brachial BP as indicated. Probability values are derived after further adjustments for the non-independence of family members.

In men, but not in women, PPc was related to LVMI independent of confounders and brachial PP and SBP (Table 2). However, no differences were noted in the strength (partial *r* values, Table 2, $P = 0.09$ using *z*-statistics) or slopes (β-coefficients, $P = 0.06$) of the brachial PP adjusted PPc–LVMI–BSA relations in men versus women. In contrast to the brachial BP-independent relations between PPc and LVMI in men, SBPc was not related to LVMI–BSA independent of brachial SBP or PP in men ($P = 0.36$–0.38) or brachial SBP in women ($P = 0.43$). Moreover, SBPc was not related to LVMI-ht$^{2.7}$ independent of brachial SBP or PP in men ($P = 0.07$–0.73) or brachial SBP in women ($P = 0.68$). These brachial BP-independent relations between PPc or SBPc and LVMI were largely reproduced in participants not receiving antihypertensive therapy and in pre- and post-menopausal women (data not shown).

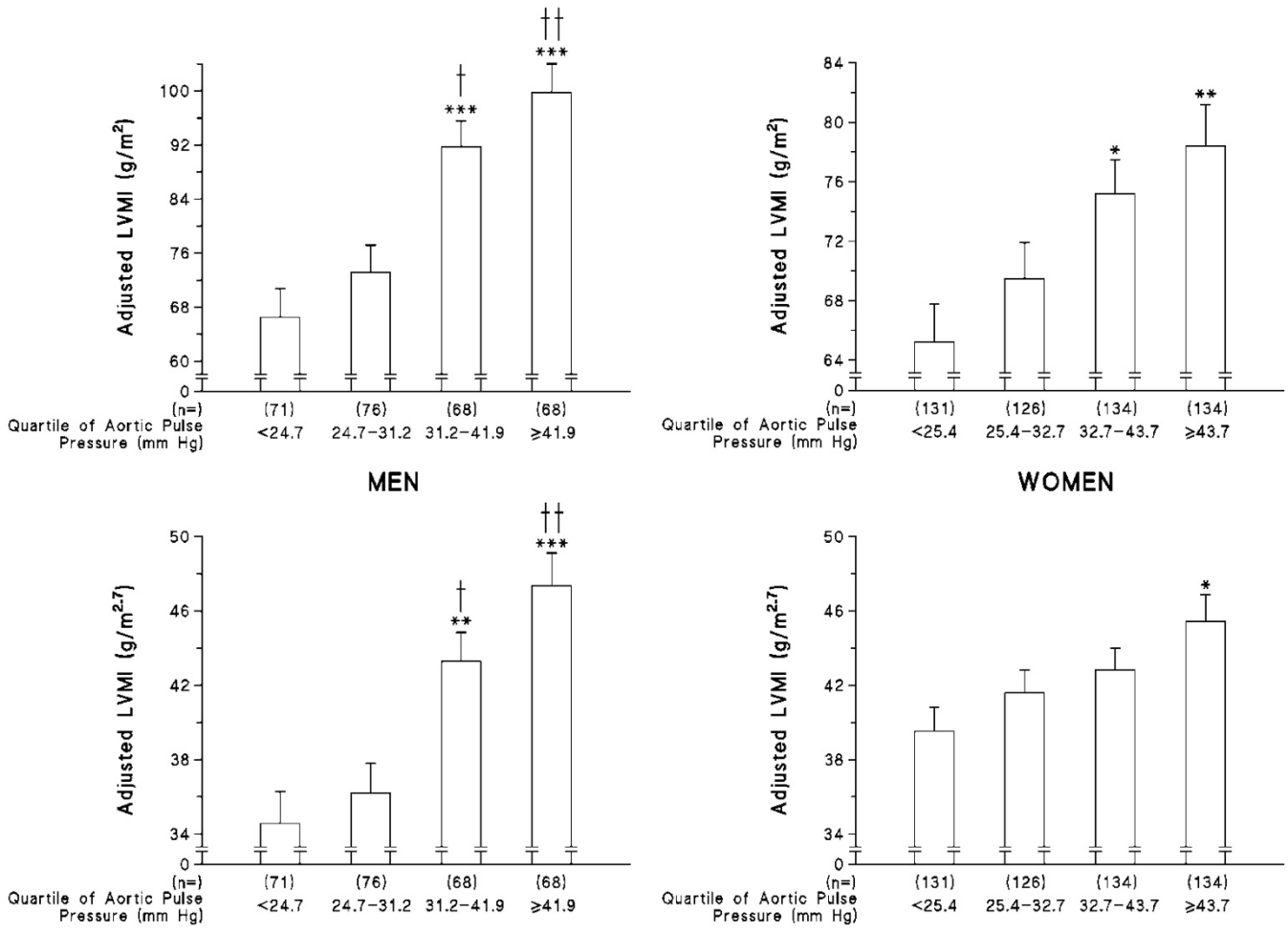

Figure 1 Multivariate adjusted left ventricular mass indexed for body surface area (BSA) (LVMI in $g\,m^{-2}$) or height$^{2.7}$ (LVMI in $g\,m^{-2.7}$) across quartiles of central aortic pulse pressure in men and women from a community sample. Adjustments are for age, mean arterial pressure, body weight, body height (for LVM indexed for BSA), the presence of diabetes mellitus or an $HbA_{1C} > 6.1\%$, pulse rate, treatment for hypertension, regular tobacco use and regular alcohol intake. Probability values are derived after further adjustments for the non-independence of family members. *P* for trend effects: LVM indexed for BSA; men, $P<0.0001$, women, $P<0.005$; LVM indexed for height$^{2.7}$; men, $P<0.0001$, women, $P<0.05$. See Table 2 for comparison of relationships between men and women. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.0001$ *vs.* quartile1, $^{\dagger}P<0.01$, $^{\dagger\dagger}P<0.0005$ *vs.* quartile 2.

Gender-specific relationships between AIx and LVMI

On bivariate analysis, AIx was associated with LVMI in both men ($P<0.0001$ for all) and women ($P<0.05$ to $P<0.0001$). However, the relationship between AIx (P_2/P_1) and LVM indexed to BSA was stronger in men ($r=0.28$, 95% confidence interval = 0.16–0.38, $P<0.0001$) as compared with women ($r=0.11$, 95% confidence interval = 0.02–0.19, $P<0.05$; $P<0.05$ for comparison of relationships using *z*-statistics). Furthermore, men showed a trend for a stronger AIx (AP/PPc)-LVM indexed for BSA relationship ($P=0.05$ for comparison of relationships) and for a stronger AIx (P_2/P_1)-LVM indexed for height$^{2.7}$ relationship ($P=0.05$ for comparison of relationships) than women.

On multivariate regression analysis independent of mean arterial pressure and alternative confounders, AIx was associated with LVMI in men, but not in women (Table 3, Figure 2). Moreover, the strength (partial r values) and the slope (β-coefficients) of the relationships between AIx and LVMI were greater in men as compared with women (Table 3). Independent relationships between AIx and LVMI were noted in neither pre-, nor postmenopausal women (Table 3). In participants not receiving antihypertensive therapy, an independent relationship between AIx (P_2/P_1) and LVMI–BSA was noted in men ($n=239$, partial $r=0.16$, $P<0.05$), whilst no relationship between AIx and LVMI–BSA was noted in women ($n=364$, partial $r=-0.02$, $P=0.76$; $P<0.05$ for comparison using z-statistics). Moreover, in participants not receiving antihypertensive therapy, a trend for an independent relationship between AIx (P_2/P_1) and LVM indexed for height$^{2.7}$ was noted in men (partial $r=0.13$, $P=0.05$), whereas no relationship between AIx and LVM indexed for height$^{2.7}$ was noted in women (partial $r=-0.003$, $P=0.96$).

Relationships between AIx and LV remodeling or LVH

In neither men (AIx (AP/PPc), odds ratio = 1.029, Wald statistics = 2.31, $P=0.13$; AIx (P_2/P_1), odds ratio = 1.013, Wald statistics = 1.70, $P=0.19$) nor in women (AIx (AP/PPc), odds ratio = 0.99, Wald statistics = 0.65, $P=0.42$; AIx (P_2/P_1), odds ratio = 1.00, Wald statistics = 0.001, $P=0.98$), was AIx independently associated with LVH (concentric + eccentric). No relations between AIx and concentric LV remodeling or AIx and the type of LVH (eccentric versus concentric) were noted in either men or women (data not shown).

Table 3 Brachial blood pressure-independent relations between aortic augmentation indices and left ventricular mass indexed to body surface area (LVMI–BSA) or height$^{2.7}$ (LVMI-ht$^{2.7}$) in men and in women from a community sample

	n	*Partial* r *(95% CI)*[a]	*β-coefficient* ± *s.e.m.*	P-*value*
Augmentation index (AP/PPc)[b] *vs. LVMI–BSA*				
Men	283	0.17[c] (0.05 to 0.28)	0.55 ± 0.20[d]	<0.01
Women	525	−0.08 (−0.16 to 0.01)	−0.20 ± 0.11	=0.08
Premenopausal women	285	0.01 (−0.11 to 0.12)	0.01 ± 0.14	=0.95
Postmenopausal women	240	−0.06 (−0.19 to 0.07)	−0.18 ± 0.21	=0.37
Augmentation index (P_2/P_1)[e] *vs. LVMI–BSA*				
Men	283	0.21[c] (0.10 to 0.32)	0.42 ± 0.12[d]	<0.0005
Women	525	−0.06 (−0.14 to 0.03)	−0.07 ± 0.05	=0.17
Premenopausal women	285	0.02 (−0.10 to 0.14)	0.02 ± 0.08	=0.77
Postmenopausal women	240	−0.03 (−0.16 to 0.10)	−0.04 ± 0.09	=0.64
Augmentation index (AP/PPc)[b] *vs. LVMI-ht$^{2.7}$*				
Men	283	0.19[c] (0.07 to 0.30)	0.25 ± 0.08[d]	<0.005
Women	525	−0.04 (−0.13 to 0.04)	−0.05 ± 0.06	=0.34
Premenopausal women	285	0.09 (−0.02 to 0.21)	0.09 ± 0.06	=0.12
Postmenopausal women	240	−0.09 (−0.21 to 0.04)	−0.15 ± 0.12	=0.19
Augmentation index (P_2/P_1)[e] *vs. LVMI-ht$^{2.7}$*				
Men	283	0.23[c] (0.11 to 0.34)	0.18 ± 0.05[d]	=0.0001
Women	525	−0.04 (−0.13 to 0.04)	−0.03 ± 0.03	=0.32
Premenopausal women	285	0.09 (−0.02 to 0.21)	0.05 ± 0.03	=0.12
Postmenopausal women	240	−0.07 (−0.20 to 0.05)	−0.06 ± 0.05	=0.26

Abbreviations: CI, confidence interval; PPc, central pulse pressure.
[a]Adjustments are for age, mean arterial pressure, body weight, height (for LVM indexed for BSA), the presence of diabetes mellitus or an HbA_{1C} > 6.1%, pulse rate, treatment for hypertension, regular tobacco use and regular alcohol intake. Probability values are derived after further adjustments for the non-independence of family members.
[b](Augmentation pressure/aortic pulse pressure) × 100.
[c]$P<0.005$ *vs.* partial *r* value for women.
[d]$P<0.005$ *vs.* β-coefficient for women.
[e](Pressure at the second systolic peak of the aortic pulse wave/pressure at the first systolic peak of the aortic pulse wave) × 100.

DISCUSSION

The main finding of the present study is that in a large, community-based sample, AIx was associated with LVMI in men, but not in women. Although there is considerable debate as to the factors that determine AIx,[3–5] this does not detract from the evidence provided from several studies demonstrating that AIx is associated with cardiovascular damage beyond brachial BP.[6–14] However, as in some studies AIx does not predict cardiovascular outcomes,[12,17,18] the possible factors that influence this relationship require identification. In this regard, although AIx predicts outcomes in men, similar relationships may be diminished in women.[10] The present study provides support for a decrease in the relationship between AIx and end-organ damage in women as compared with men. This is in contrast to the comparable unadjusted relations previously demonstrated between AIx and LVMI or alternative end-organ changes between men and women in a large community-based study.[10] However, whether in that study[10] similar relations between AIx and end-organ changes were also noted in men and women after multivariate adjustments is unclear.[10]

Previous studies that have demonstrated that AIx derived from radial applanation tonometry is independently associated with LVM reduction, or LVH,[13,14] were not statistically powered to report on whether these associations were sex specific. Interestingly, however, in both studies, 70% or more of the study participants were men.[13,14] Hence, both of these studies[13,14] may reflect a dominant impact of AIx on LVMI in men.

An explanation for the gender-specific impact on relations between AIx and LVMI noted in the present study, or between AIx and cardiovascular outcomes in a previous study,[10] requires consideration. In this regard, in contrast to what was previously thought, AIx is not an appropriate index of wave reflection.[3–5] Rather, unlike more suitable indices of wave reflection, AIx may be influenced by aortic reservoir function,[3] left ventricular systolic function,[4] as well as height and female gender.[3] Some of these factors may have little impact on cardiovascular risk. Indeed, measures of reflective wave function are better risk markers than AIx.[10,17] Alternatively, although aortic PP is associated with cardiovascular damage, reflective wave function may contribute little toward the impact of aortic PPc on cardiovascular damage in women. Indeed, in a large, community-based study, both AIx and the reflection index predicted cardiovascular outcomes in men, but not in women.[10] Hence, further studies are required to establish whether the sex-specific relations between AIx and LVMI or alternative end-organ changes are attributed to the poor relationship between AIx and reflective wave function,[3–5] or to the lack of impact of reflective waves on end-organ changes in women as compared to men.

Several differences were noted between men and women in the present study, differences which may account for the sex-specific effects of AIx on LVMI. In this regard, more women than men were obese or had diabetes mellitus or an abnormal HbA1c and hence obesity or diabetes mellitus may have a more important role than BP in mediating increases in LVMI in women. In addition, although a similar proportion of men and women were hypertensive, fewer hypertensive men were receiving antihypertensive medication. Hence, the sensitivity to detect an impact of AIx on LVMI may have been greater in men than in women.

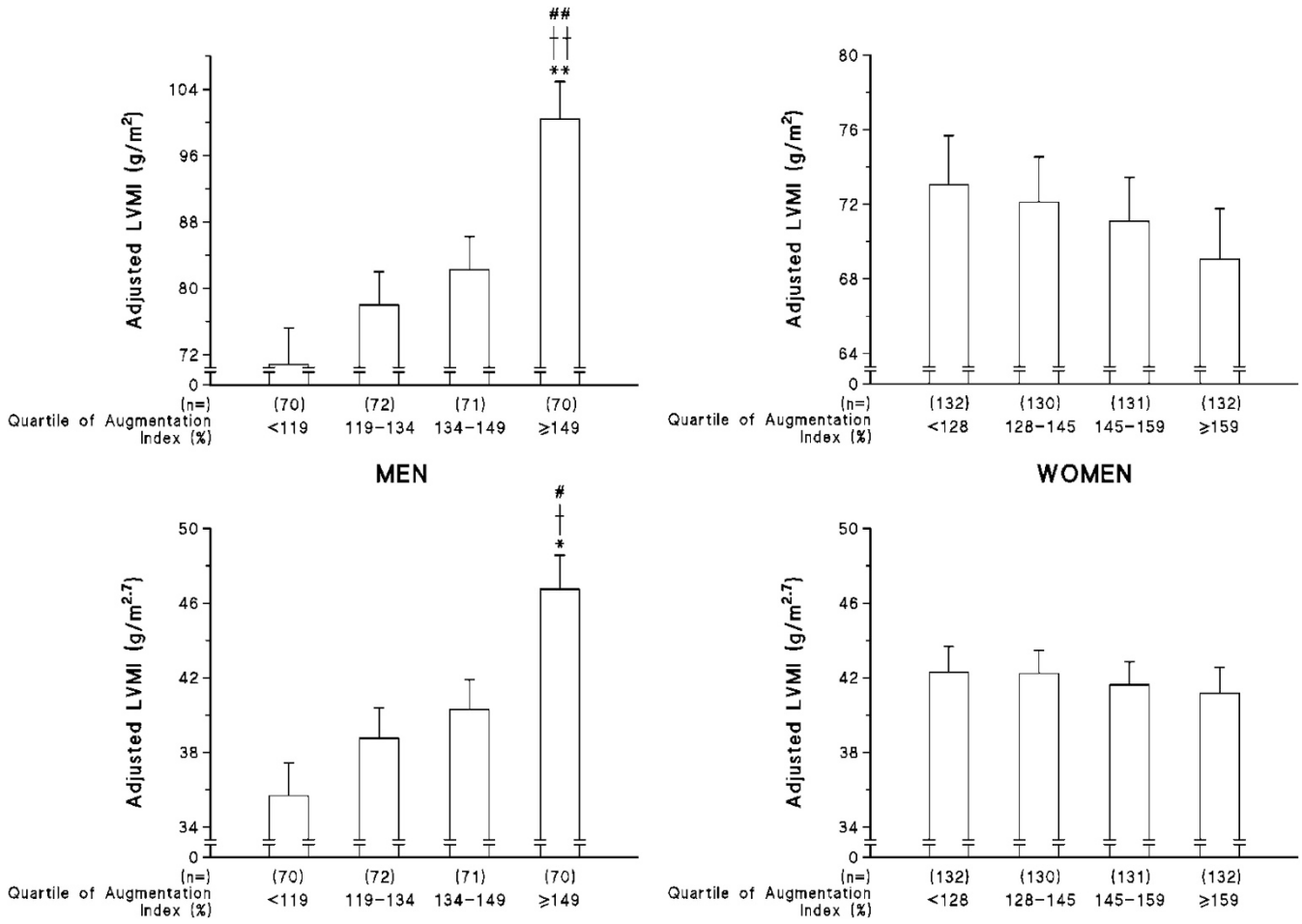

Figure 2 Multivariate adjusted left ventricular mass indexed for body surface area (BSA) (LVMI in $g\,m^{-2}$) or height$^{2.7}$ (LVMI in $g\,m^{-2.7}$) across quartiles of aortic augmentation index ((pressure at the second systolic peak of the aortic pulse wave/pressure at the first systolic peak of the aortic pulse wave) × 100) in men and women from a community sample. Adjustments are for age, mean arterial pressure, body weight, body height (for LVM indexed for BSA), the presence of diabetes mellitus or an $HbA_{1C} > 6.1\%$, pulse rate, treatment for hypertension, regular tobacco use and regular alcohol intake. Probability values are derived after further adjustments for the non-independence of family members. *P* for trend effects: LVM indexed for BSA; men, $P<0.0005$, women, $P=0.17$; LVM indexed for height$^{2.7}$; men, $P=0.0001$, women, $P=0.32$. See Table 2 for comparison of relationships between men and women. $^{*}P<0.001$, $^{**}P<0.0005$ vs. quartile1, $^{\dagger}P<0.05$, $^{\dagger\dagger}P<0.005$ *vs.* quartile 2, $^{\#}P<0.05$, $^{\#\#}P<0.01$ *vs.* quartile 3.

The clinical implication of the present study is that when considering the contribution of central aortic haemodynamic measurements as predictors of cardiovascular damage, AIx may serve as an appropriate predictor in men, but not in women. Hence, in women, either aortic BP *per se* may be a better aortic haemodynamic index to predict damage beyond brachial BP, or wave separation analysis may be required to identify the impact of reflective waves on cardiovascular damage.

The limitations of the present study are as follows: first, the cross-sectional nature of the study precludes conclusions being drawn regarding cause and effect. Second, in the present study, calibration of the radial waveform from brachial BP measurements ignores amplification of BP from brachial to radial arteries. Hence, aortic pressures are likely to have been underestimated using the current approach. Third, because the present study was community based, only a small proportion of participants had LVH. Hence, we were not statistically powered to show sex-specific relations between AIx and LVH. Thus, further studies are necessary in untreated hypertensives to evaluate whether the relationship between AIx and LVH is sex-specific. Last, the present study was conducted in one ethnic group. Hence further studies in communities of alternative ethnic origins are required.

In conclusion, in the present study, we show that despite an independent relationship between aortic BP and LVMI in both men and women, AIx is independently associated with LVMI in men, but not in women. These data suggest that AIx may not be an appropriate predictor of the extent of cardiovascular end-organ changes in women.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study would not have been possible without the voluntary collaboration of the participants and the excellent technical assistance of Mthuthuzeli Kiviet, Nomonde Molebatsi and Nkele Maseko. This study was supported by the Medical Research Council of South Africa, the University Research Council of the University of the Witwatersrand, the National Research Foundation (Women in Research and the Thuthuka Program), the Circulatory Disorders Research Trust and the Carnegie Corporation.

1 Aviolo AP, van Bortel LM, Boutouyrie P, Cockcroft J, McEniery CM, Progerou AD, Roman MJ, Safar ME, Segers P, Smulyan H. Role of pulse pressure amplification in arterial hypertension: experts opinion and review of the data. *Hypertension* 2009; **54**: 375–383.
2 Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, Wang J-G, Wilkinson IB, Williams B, Vlachopoulos C. Central blood pressure measurements and antihypertensive therapy. A consensus document. *Hypertension* 2007; **50**: 154–160.
3 Davies JE, Baksi J, Francis DP, Hadjiloizou N, Whinnett ZI, Manisty CH, Aguado-Sierra J, Foale RA, Malik IS, Tyberg JV, Parker KH, Mayet J, Hughes AD. The arterial reservoir and pressure increases with aging and is the major determinant of aortic augmentation index. *Am J Physiol Heart Circ* 2010; **298**: H580–H586.
4 Cheng K, Cameron JD, Tung M, Mottram PM, Meredith IT, Hope SA. Association of left ventricular motion and central augmentation index in healthy young men. *J Hypertens* 2012; **30**: 2395–2402.
5 Hughes AD, Park C, Davies J, Francis D, McG Thom SA, Mayet J, Parker KH. Limitations of augmentation index in the assessment of wave reflection in normotensive healthy individuals. *PLoS ONE* 2013; **8**: e59371.
6 London GM, Blacher J, Pannier B, Guérin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. *Hypertension* 2001; **38**: 434–438.
7 Ueda H, Hayashi T, Tsumura K, Yoshimaru K, Nakayama Y, Yoshikawa J. The timing of the reflected wave in the ascending aortic pressure predicts restenosis after coronary stent placement. *Hypertens Res* 2004; **27**: 535–540.
8 Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Lamm G, Stark N, Rammer M, Eber B. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *Eur Heart J* 2005; **26**: 2657–2663.
9 Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Willens HJ, Perez G, Mendez AJ. Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. *Hypertension* 2005; **45**: 980–985.
10 Wang K-L, Cheng H-M, Sung S-H, Chuang S-Y, Hung C-H, Spurgeon HA, Ting C-T, Najjar SS, Lakatta EG, Yin FCP, Chou P, Chen C-H. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. *Hypertension* 2010; **55**: 799–805.
11 Chirinos JA, Kips JG, Jacobs Jr DR, Brumback L, Duprez DA, Kronmal R, Bluemke DA, Townsend RR, Vermeersch S, Segers P. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2012; **60**: 2170–2177.
12 Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J* 2010; **31**: 1865–1871.
13 Hashimoto J, Imai J, O' Rourke MF. Indices of pulse wave analysis are better predictors of left ventricular mass reduction than cuff pressure. *Am J Hypertens* 2007; **20**: 378–384.
14 Hashimoto J, Watabe D, Hatanaka R, Hanasawa T, Metoki H, Asayama K, Ohkubo T, Totsune K, Imai Y. Enhanced radial late systolic pressure augmentation in hypertensive patients with left ventricular hypertrophy. *Am J Hypertens* 2006; **19**: 27–32.
15 Weber T, Auer J, O'Rourke MF, Punzengruber C, Kvas E, Eber B. Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction. *Heart* 2006; **92**: 1616–1622.
16 Westerbacka J, Leinonen E, Salonen JT, Salonen R, Hiukka A, Yki-Jarvinen H, Taskinen M-R. Increased augmentation of central blood pressure is associated with increases in carotid intima-media thickness in type 2 diabetic patients. *Diabetologia* 2005; **48**: 1654–1662.
17 Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010; **121**: 505–511.
18 Hayashi S, Yamada H, Bando M, Hotchi J, Ise T, Yamaguchi K, Iwase T, Soeki T, Wakatsuki T, Tamaki T, Sato M. Augmentation index does not reflect risk of coronary artery disease in elderly patients. *Circ J* 2014; **78**: 1176–1182.
19 Mitchell GF, Wang N, Palmisano JN, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin E, Vasan RS. Hemodynamic correlates of blood pressure across the adult age spectrum. *Circulation* 2010; **122**: 1379–1386.
20 Casale PN, Devereux RB, Milner M, Zullo G, Harshfield GA, Pickering TG, Laragh JH. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med* 1986; **105**: 173–178.
21 Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *New Engl J Med* 1990; **322**: 1561–1566.
22 Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; **114**: 345–352.
23 Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994; **90**: 1786–1793.
24 Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, Santucci A, Santucci C, Reboldi G, Porcellati C. Prognostic value of left ventricular mass and geometry in systemic hypertension with left ventricular hypertrophy. *Am J Cardiol* 1996; **78**: 197–202.
25 Ghali JK, Liao Y, Cooper RS. Influence of left ventricular geometric patterns on prognosis in patients with or without coronary artery disease. *J Am Coll Cardiol* 1998; **31**: 1635–1640.
26 Devereux RB, Wachtell K, Gerdts E, Boman K, Nieminen MS, Papademetriou V, Rokkedal J, Harris K, Aurup P, Dahlof B. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA* 2004; **292**: 2350–2356.
27 Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snapinn S, Harris KE, Aurup P, Edelman JM, Wedel H, Lindholm LH, Dahlof B, for LIFE Study Investigators. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; **292**: 2343–2349.
28 Norton GR, Maseko M, Libhaber E, Libhaber CD, Majane OHI, Dessein P, Sareli P, Woodiwiss AJ. Is pre-hypertension an independent predictor of target organ changes in young-to-middle aged persons of African descent? *J Hypertens* 2008; **26**: 2279–2287.
29 Woodiwiss AJ, Molebatsi N, Maseko MJ, Libhaber E, Libhaber C, Majane OHI, Paiker J, Dessein P, Brooksbank R, Sareli P, Norton GR. Nurse-recorded auscultatory blood pressure at a single visit predicts target organ changes as well as ambulatory blood pressure. *J Hypertens* 2009; **27**: 287–297.
30 Redelinghuys M, Norton GR, Scott L, Maseko MJ, Brooksbank R, Majane OHI, Sareli P, Woodiwiss AJ. Relationship between urinary salt excretion and pulse pressure and central aortic hemodynamics independent of steady state pressure in the general population. *Hypertension* 2010; **56**: 584–590.
31 Norton GR, Majane OH, Maseko MJ, Libhaber C, Redelinghuys M, Kruger D, Veller M, Sareli P, Woodiwiss AJ. Brachial blood pressure-independent relations between radial late systolic shoulder-derived aortic pressures and target organ changes. *Hypertension* 2012; **59**: 885–892.
32 Chirinos JA, Kips JG, Roman MJ, Medina-Lezama J, Li Y, Woodiwiss AJ, Norton GR, Yasmin, Van Bortel L, Wang J-G, Cockroft JR, Devereux RB, Wilkinson IB, Segers P, McEniery CM. Ethnic differences in arterial wave reflections and normative equations for augmentation index. *Hypertension* 2011; **57**: 1108–1116.
33 Sahn DJ, De Maria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurement. *Circulation* 1978; **58**: 1072–1083.
34 Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiograph assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **57**: 450–458.