

## ORIGINAL ARTICLE

# Sex-specific hemodynamic and non-hemodynamic determinants of aortic root size in hypertensive subjects with left ventricular hypertrophy

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**Aortic root (AoR) dilatation is more frequently observed in hypertensive individuals and is independently associated with left ventricular (LV) hypertrophy. Although the LV structure has sex-specific predictors, it remains unknown whether there are gender-related differences in the determinants of AoR size. We carried out a cross-sectional analysis of clinical, laboratory, anthropometric, fundoscopic and echocardiographic features of 438 hypertensive patients with LV hypertrophy (266 women and 172 men). Women with enlarged AoR had higher cardiac output ( $P=0.0004$ ), decreased peripheral vascular resistance ( $P=0.009$ ), higher prevalence of mild aortic regurgitation ( $P=0.02$ ) and increased waist circumference ( $P=0.04$ ), whereas AoR-dilated men presented with a higher prevalence of concentric LV hypertrophy ( $P=0.0008$ ) and mild aortic regurgitation ( $P=0.005$ ) and increased log C-reactive protein levels ( $P=0.02$ ), compared with sex-matched normal AoR subjects. In women, AoR dilatation associated with cardiac output, mild aortic regurgitation and waist circumference in a multivariate model including age, body surface area, height, homeostasis model assessment index, LV mass index, diastolic blood pressure, menopause status and use of antihypertensive medications as independent variables. Conversely, AoR dilatation associated with LV relative wall thickness, log C-reactive protein and mild aortic regurgitation without contributions from diastolic blood pressure, height, body surface area, LV mass index, peripheral vascular resistance and antihypertensive medications in men. Taken together, these results suggest that both volume overload and abdominal obesity are related to AoR dilatation in hypertensive women, whereas AoR enlargement is associated more with inflammatory and myocardial growth-related parameters in hypertensive men with LV hypertrophy.**

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**Keywords:** aortic root; gender; left ventricular hypertrophy; volume overload

## INTRODUCTION

Dilatation of the aortic root (AoR) is frequently associated with higher cardiovascular mortality.<sup>1,2</sup> Therefore, increased importance has been devoted to the study of the biological determinants of AoR size. AoR dilatation is observed more frequently in hypertensive than in normotensive individuals<sup>3,4</sup> and its prevalence is higher in patients with complicated hypertension,<sup>5–7</sup> supporting the idea that it is a target-organ damage marker. However, this assumption has been challenged by several lines of evidence showing no difference in AoR diameter between hypertensive and normotensive individuals after adjusting for age and body size.<sup>3,4,8</sup>

Left ventricular (LV) hypertrophy is a major predictor of AoR dilatation in hypertensive subjects, independent of age, body size and gender.<sup>6,7</sup> This observation argues against the notion that changes in AoR diameter are solely explained by variations in body size and age,

and points toward AoR and LV remodeling as processes with common pathophysiological mechanisms. In addition, it suggests that hypertensive patients with LV hypertrophy comprise a population with attractive features for the study of potential determinants of AoR size.

Mounting evidence showed that there are gender-related differences in the predictors of LV structure in hypertensive subjects. In this regard, LV mass and geometry show sex-specific relationships with body mass composition, metabolic factors and other markers of target-organ damage.<sup>9–12</sup> On the other hand, AoR size and the prevalence of AoR dilatation are clearly higher in men,<sup>4–6</sup> indicating that gender has a major role in the regulation of the AoR phenotype. Nevertheless, it remains unknown whether there are sex-related differences in the determinants of AoR diameter in hypertensive subjects. Therefore, the aim of this study was to evaluate the impact

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of gender on the determinants of AoR size in a sample of patients with hypertension and LV hypertrophy.

## METHODS

A total of 438 consecutive patients (325 Whites and 113 Blacks), followed up at the Hypertension Unit of the University of Campinas, were included in the study. Inclusion criteria were as follows: (1) hypertension, defined as systolic blood pressure  $\geq 140$  mmHg, or diastolic blood pressure  $\geq 90$  mmHg or current antihypertensive medication use; (2) echocardiographic diagnosis of LV hypertrophy; and (3) age over 18 years and no evidence of moderate or severe cardiac valve disease, hypertrophic cardiomyopathy, previous myocardial infarction, neoplastic disease and suspected secondary hypertension. The studied patients underwent a cross-sectional analysis of the following diagnostic procedures: (1) clinical blood pressure measurements, (2) anthropometric measurements, (3) routine investigations (blood chemistry, creatinine clearance and urinary albumin–creatinine ratio analyses), (4) funduscopic examination and (5) an echocardiogram. The study was approved by the ethics committee of the University of Campinas, and written consent was obtained from all participants.

Blood pressure was measured using a validated digital oscillometric device (Omron HEM-705CP, Omron Healthcare, Kyoto, Japan) with appropriate cuff sizes.<sup>10</sup> Body mass index was calculated as body weight divided by height squared (expressed in  $\text{kg m}^{-2}$ ). Waist circumference was measured at the midpoint between the lowest rib and iliac crest and hip circumference at the level of the greater trochanters.

Blood samples were obtained in the morning after 12 h of fasting for analysis of total cholesterol, cholesterol fractions, glucose, insulin and C-reactive protein levels. The homeostasis model assessment index was calculated as follows:  $\text{glucose (mg per 100 ml)} \times \text{insulin } (\mu\text{U ml}^{-1}) / 405$ .<sup>10</sup> Funduscopic diagnosis of hypertensive retinopathy was evaluated bilaterally by a skilled ophthalmologist, who had no knowledge of the patient's clinical characteristics. The funduscopic findings were graded using the Keith–Wagener classification. Albuminuria was evaluated in patients by measuring the albumin–creatinine ratio in morning urine samples. In addition, creatinine clearance was also measured. Diabetes mellitus was diagnosed if fasting blood glucose was  $\geq 126$  mg per 100 ml or when participants were taking hypoglycemic medications, whereas metabolic syndrome was defined in accordance with the National Cholesterol Education Program Panel III criteria.<sup>13</sup> Women with reported amenorrhea for more than 12 months, except for pregnancy, were identified as postmenopausal.

Echocardiography studies were conducted on each subject at rest in the left lateral decubitus position using a Vivid 3 Pro (General Electric, Milwaukee, WI, USA) apparatus equipped with a 2.5-MHz transducer as described previously.<sup>14</sup> AoR diameter, LV end-diastolic and end-systolic diameters, interventricular septum thickness, posterior wall thickness and LV mass were measured in accordance with the American Society of Echocardiography guidelines.<sup>15</sup> AoR diameter was measured at the level of Valsalva's sinuses by M-mode tracings, under two-dimensional control, as the maximal distance between the two leading edges of the anterior and posterior AoR walls at the end diastole. Relative wall thickness was computed as twice the posterior wall thickness divided by the LV end-diastolic diameter. Mild aortic regurgitation was identified on the basis of the extent of diastolic turbulent flow in the LV, indicated by a variance signal, by a jet occupying  $< 20\%$  of the aortic annular diameter at its origin and extending less than halfway to the tip of the anterior mitral leaflet.<sup>16</sup> All the recordings were made by the same physician, who was unaware of other data relating to the subjects. The reproducibility of both acquiring and measuring LV mass and AoR size was determined in recordings obtained from 10 subjects. Intraobserver LV mass and AoR size variabilities were  $< 8$  and  $< 3\%$ , respectively, whereas interobserver variabilities of these parameters were  $< 11$  and  $< 5\%$ , respectively.

Systolic volume was generated from Doppler interrogation of transaortic flow at the aortic annular level and aortic valve cross-sectional area.<sup>17</sup> Cardiac output was calculated as systolic volume  $\times$  cardiac frequency, whereas peripheral vascular resistance was obtained using the formula: mean blood pressure / cardiac output.

Aortic root was considered dilated when its diameter was  $\geq 37$  mm in women and 40 mm in men. These cutoff points were the 98th percentile ( $> 2$

s.d.) values<sup>7</sup> in a group of 356 normotensive, non-obese (body mass index between 20 and 25  $\text{kg m}^{-2}$ ) and apparently normal adults (196 women and 160 men; mean age:  $56.0 \pm 0.6$  years) evaluated in an outpatient unit for a cardiovascular checkup in the previous 3 years. LV hypertrophy was defined with the use of cutoff point  $\text{LV mass/height}^{2.7} > 51$  for both genders,<sup>18</sup> whereas concentric geometry was considered if the relative wall thickness was  $\geq 0.45$ .<sup>19</sup>

Descriptive statistical results are expressed as mean  $\pm$  s.e. Chi-squared test was used to compare categorical variables, whereas the unpaired *t*-test and Mann–Whitney test compared the parametric and nonparametric continuous variables, respectively. Pearson's or Spearman's method was used to assess univariate correlations between clinical features and AoR size. Stepwise and logistic regression analyses evaluated the independent determinants of AoR diameter. A *P*-value  $< 0.05$  was considered significant.

## RESULTS

### Gender-specific features of hypertrophic patients according to AoR dilatation

Aortic root dilatation, defined by the sex-specific criteria of 40 mm in men and 37 mm in women, was found in 46 of 438 patients, with an overall prevalence rate of 10.5%. A dilated AoR was present in 15.1% of men and in 7.5% of women. The clinical features of the studied subjects are presented in Table 1. Women and men with AoR enlargement were older than those with normal AoR size, whereas larger waist circumference and higher prevalence of postmenopause were found in females with dilated AoR compared with normal AoR women. Conversely, men with AoR dilatation showed higher log C-reactive protein levels compared with those with normal AoR size. Body surface area, body mass index, hip circumference, homeostasis model assessment index and use of antihypertensive medications were similar in both genders according to AoR size. In addition, subjects with AoR dilatation showed no differences in lipid fractions and in the prevalence of smoking and diabetes mellitus (Supplementary data).

Table 2 shows the echocardiographic features of men and women, as well as their statistical comparisons according to the presence or absence of AoR dilatation. Men with AoR dilatation showed increased LV wall thickness, relative wall thickness, LV mass index and a higher prevalence of LV concentric hypertrophy, whereas women with enlarged AoR displayed increased LV end-diastolic diameter compared with sex-matched subjects with normal AoR size. Moreover, subjects with AoR dilatation of both genders showed increased prevalence of mild aortic regurgitation. In contrast to LV structural parameters, no variations in retinal vascular changes, as well as in urinary albumin–creatinine ratio and creatinine clearance, were found in both genders according to the presence or absence of AoR enlargement (Supplementary data).

The hemodynamic features of studied subjects are shown in Table 3. Women with enlarged AoR showed higher stroke volume and cardiac output in addition to lower peripheral vascular resistance than did those with normal AoR size. On the other hand, no differences in hemodynamic parameters were found in men according to AoR size.

### Univariate correlations between AoR size and studied variables

To determine the sex-specific correlates of AoR size, univariate analyses were carried out (Table 4). In hypertensive women, AoR size showed a positive and major correlation with LV end-diastolic diameter, waist circumference, LV mass index, stroke volume and cardiac output and displayed a weaker direct relationship with age, body surface area, hip circumference, body mass index, LV wall thickness, postmenopause, mild aortic regurgitation and height.

**Table 1 Clinical characteristics of subjects with aortic root dilatation**

Variables	Women		Men	
	Normal (n=246)	Dilated (n=20)	Normal (n=146)	Dilated (n=26)
Age, years	56.8±0.9	62.0±1.7*	56.9±1.1	61.9±1.3*
Whites, n (%)	182 (74)	16 (80)	110 (75)	17 (65)
Body mass index, kg m <sup>-2</sup>	31.4±0.3	32.4±0.9	31.1±0.4	31.3±0.8
Body surface area, m <sup>2</sup>	1.68±0.02	1.76±0.03	1.95±0.02	1.97±0.04
Height, m	1.55±0.01	1.55±0.02	1.69±0.02	1.66±0.02
Waist circumference, cm	100.0±0.8	106.1±2.3*	104.9±1.0	104.8±2.3
Hip circumference, cm	106.6±1.0	111.2±2.3	105.9±0.8	105.6±1.6
Metabolic syndrome, n (%)	155 (63)	15 (75)	95 (65)	17 (65)
Postmenopause	177 (72)	19 (95)*	—	—
HOMA	4.1±0.3	3.3±0.5	3.9±0.3	3.8±0.9
Log CRP, mg per 100 ml	-0.43±0.03	-0.27±0.14	-0.55±0.04	-0.30±0.11**
Diuretics, n (%)	190 (77)	15 (75)	117 (80)	21 (81)
β-Blockers, n (%)	116 (47)	8 (40)	73 (50)	11 (42)
CCB, n (%)	113 (46)	12 (60)	63 (43)	14 (54)
ACEI or ARB, n (%)	202 (82)	17 (85)	126 (86)	23 (88)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AoR, aortic root; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CRP, C-reactive protein; HOMA, homeostasis model assessment index.

\*P=0.04 and \*\*P=0.02 compared with sex-matched subjects with normal AoR size.

**Table 2 Echocardiographic features of subjects with aortic root dilatation**

Variables	Women			Men		
	Normal (n=246)	Dilated (n=20)	P-value	Normal (n=146)	Dilated (n=26)	P-value
Aorta, mm	31.2±0.2	38.7±0.5	<0.0001	34.2±0.2	42.0±0.4	<0.0001
LV end-diastolic diameter, mm	48.8±0.3	52.3±1.3	0.002	53.0±0.5	53.1±1.0	NS
Posterior wall thickness, mm	11.0±0.1	10.9±0.3	NS	11.5±0.1	12.6±0.2	0.0002
Interventricular septum, mm	11.1±0.1	11.2±0.4	NS	11.6±0.1	12.9±0.2	<0.0001
Relative wall thickness	0.45±0.01	0.42±0.02	NS	0.44±0.01	0.47±0.01	0.009
LV concentric hypertrophy, n (%)	108 (44)	5 (25)	NS	55 (38)	19 (73)	0.0008
LV mass index, g/h <sup>2.7</sup>	79.8±1.5	86.8±4.5	NS	78.6±1.7	88.4±2.8	0.02
Ejection fraction, %	66.2±0.4	65.3±2.1	NS	62.6±0.8	62.4±1.5	NS
Mild aortic regurgitation, n (%)	45 (18)	8 (40)	0.02	30 (21)	12 (46)	0.005

Abbreviations: LV, left ventricular; NS, nonsignificant.

**Table 3 Hemodynamic features of subjects with aortic root dilatation**

Variables	Women			Men		
	Normal (n=246)	Dilated (n=20)	P-value	Normal (n=146)	Dilated (n=26)	P-value
Systolic blood pressure, mm Hg	152.1±1.9	143.6±4.5	NS	149.7±2.1	152.5±5.0	NS
Diastolic blood pressure, mm Hg	89.1±1.1	84.1±3.3	NS	88.4±1.2	88.7±2.5	NS
Heart rate, b.p.m.	65.1±0.4	67.3±1.4	NS	64.5±0.6	63.3±1.6	NS
Stroke volume, ml	82.3±1.2	95.5±6.0	0.003	92.9±1.8	93.6±3.7	NS
Cardiac output, l per min	5.34±0.08	6.33±0.32	0.0004	5.97±0.12	5.92±0.26	NS
Peripheral vascular resistance, dynes sec cm <sup>-5</sup>	1716±38	1381±77	0.009	1549±40	1594±121	NS

Abbreviations: b.p.m., beats per minute; NS, nonsignificant.

Conversely, AoR size correlated inversely with the peripheral vascular resistance and ejection fraction in this gender. In men, AoR diameter correlated directly with the LV wall thickness, LV mass index, mild aortic regurgitation, relative wall thickness, age, log C-reactive protein and peripheral vascular resistance. Finally, no significant relationship was observed between AoR size and creatinine clearance, log urinary albumin-creatinine, retinal vascular changes, lipid fractions, smoking,

diabetes mellitus or antihypertensive medications in both genders (data not shown).

#### Multivariate determinants of AoR size and dilatation

Stepwise and logistic regression analyses were carried out to evaluate the independent contributions of different factors to AoR size and AoR dilatation, respectively. In women, AoR size associated with

**Table 4 Univariate correlation analysis of aortic root size**

Variables	Women (n=266)	Men (n=172)
Age	0.16*	0.22*
Body surface area	0.22**	-0.02
Body mass index	0.17*	0.01
Height	0.14***	-0.02
Waist circumference	0.29**	0.06
Hip circumference	0.22**	0.03
Systolic blood pressure	-0.06	0.02
Diastolic blood pressure	-0.06	0.08
Metabolic syndrome	0.07	0.08
Postmenopause	0.14***	—
Homeostasis model assessment index	-0.03	-0.02
Log C-reactive protein	0.04	0.16***
Left ventricular end-diastolic diameter	0.35**	0.02
Posterior wall thickness	0.15***	0.35**
Interventricular septum	0.15***	0.38**
Relative wall thickness	-0.07	0.26**
Left ventricular mass index	0.27**	0.29**
Ejection fraction	-0.16*	-0.08
Mild aortic regurgitation	0.14***	0.29**
Stroke volume	0.26**	-0.13
Cardiac output	0.24**	-0.13
Peripheral vascular resistance	-0.20**	0.16***

\* $P < 0.01$ ; \*\* $P < 0.001$ ; \*\*\* $P < 0.05$ .

**Table 5 Regression analyses of the association between selected independent variables and AoR size/dilatation in hypertensive women**

Step	Variables	R <sup>2</sup> change	P-value
<i>Dependent: AoR size (model 1)</i>			
1	Cardiac output	0.040	0.0008
2	Waist circumference	0.035	0.001
3	Mild aortic regurgitation	0.025	0.007
4	Age	0.017	0.02
5	Left ventricular mass index	0.015	0.03
6	Height	0.013	0.04
<i>Dependent: AoR dilatation (model 2)</i>			
		<i>Hazard ratio</i>	
1	Cardiac output >5.5 l per min	5.80	0.004
2	Mild aortic regurgitation	3.87	0.02
3	Waist circumference >105 cm	3.46	0.03

Abbreviation: AoR, aortic root. Independent variables in model 1 also included body surface area, diastolic blood pressure, menopause status, homeostasis model assessment index and use of antihypertensive medications. In model 2, age >60 years, height >1.55 m, body surface area >1.70 m<sup>2</sup>, diastolic blood pressure >90 mm Hg, left ventricular mass index >80 g/h<sup>2.7</sup>, menopause status, homeostasis model assessment index >3.5 and use of antihypertensive medications were also included as independent variables. Only variables with significant association are presented.

cardiac output, waist circumference, mild aortic regurgitation, age, LV mass index and height, whereas cardiac output, mild aortic regurgitation and waist circumference were independently related to AoR dilatation in this gender (Table 5). In men, both AoR size and AoR dilatation associated with mild aortic regurgitation, relative wall thickness and log C-reactive protein (Table 6).

**DISCUSSION**

In this report, we evaluated a sample of hypertensive patients with LV hypertrophy and found that (1) AoR size and dilatation were paralleled

**Table 6 Regression analyses of the association between selected independent variables and AoR size/dilatation in hypertensive men**

Step	Variable	R <sup>2</sup> change	P-value
<i>Dependent: AoR size (model 1)</i>			
1	Mild aortic regurgitation	0.111	0.00002
2	Relative wall thickness	0.071	0.0003
3	Log C-reactive protein	0.037	0.007
<i>Dependent: AoR dilatation (model 2)</i>			
		<i>Hazard ratio</i>	
1	Relative wall thickness ≥0.45	11.65	0.0002
2	Log C-reactive protein >-0.41 mg per 100 ml	6.77	0.002
3	Mild aortic regurgitation	5.84	0.007

Abbreviation: AoR, aortic root. Independent variables in model 1 also included age, height, body surface area, diastolic blood pressure, left ventricular mass index, peripheral vascular resistance and use of antihypertensive medications. In model 2, age >60 years, height >1.66 m, body surface area >1.95 m<sup>2</sup>, diastolic blood pressure >90 mm Hg, left ventricular mass index >80 g/h<sup>2.7</sup>, peripheral vascular resistance >1550 dynes sec cm<sup>-5</sup> and use of antihypertensive medications were also included as independent variables. Only variables with significant association are presented.

by higher cardiac output and increased waist circumference in women; (2) LV concentric hypertrophy and C-reactive protein were independently associated with AoR size and dilatation in hypertensive men; and (3) although LV mass associated with AoR diameter in both genders, LV end-diastolic diameter and LV wall thickness were actually the foremost correlates of AoR size in women and men, respectively. Overall, these findings suggest that gender-specific mechanisms might be implicated in the regulation of AoR size in hypertensive subjects with LV hypertrophy.

In our study, hypertensive women with AoR dilatation showed increased stroke volume and cardiac output as well as reduced peripheral vascular resistance compared with those with normal AoR. Accordingly, cardiac output emerged as an independent determinant of female AoR size after multivariate analysis. These results point toward a role of volume load in the regulation of AoR diameter in this gender. In agreement with this assumption, larger AoR diameters have been described in individuals with volume overload, such as marathon runners and patients with anemia and aortic valve regurgitation.<sup>20-22</sup> Moreover, results of the LIFE study showed that stroke volume, a putative marker of volume load, was an independent predictor of AoR diameter, strengthening the notion that proximal aortic structure is sensitive to changes in volume status in hypertensive subjects.<sup>5</sup> One potential cause of volume overload in hypertensive patients is obesity.<sup>23</sup> In fact, in our study, AoR size was shown to correlate with body mass index and body surface area in women. Nonetheless, the present findings indicated that abdominal rather than global obesity was more related to AoR size in this gender. In this context, waist circumference came up as the anthropometric measurement showing the strongest correlation with AoR size and was independently associated with AoR diameter. Noticeably, the relationship between waist circumference and AoR size was independent of the homeostasis model assessment index, suggesting that insulin resistance had no major role in this regard. These results are in agreement with a recent report from our group showing that waist circumference was associated with the LV end-diastolic diameter independently of insulin resistance and body mass index in hypertensive women with a high prevalence of LV hypertrophy.<sup>10</sup> Altogether, these data seem to suggest that circulating volume derived from central adiposity might be involved in AoR and LV chamber enlargement in hypertensive women. Conversely, although the relationship between AoR size and cardiac output and central

obesity was not influenced by menopause status, we cannot rule out the role of estrogens in this regard.

In contrast to the results obtained from females, LV concentric hypertrophy showed a major relationship with AoR size in males. Similarly, the positive association between LV mass and AoR size was mainly dependent on LV wall thickness in men, whereas it was mostly reliant on LV chamber diameter in women. These findings might provide some clues regarding the regulatory mechanisms of male AoR size. First, they indicate that growth factors influencing the myocardium may be also involved in AoR remodeling. Second, they suggest that pressure overload might be a potential hemodynamic stimulus for AoR dilatation, given that hypertension is strongly related to LV concentricity.<sup>24</sup> Traditionally, chronic exposure to high intra-arterial pressures in hypertension is believed to accelerate elastin breakdown, and is therefore believed to further promote proximal aortic dilatation.<sup>25</sup> However, this assumption is challenged by the absence of a significant relationship between blood pressure and AoR size in our studied sample. Although the use of antihypertensive medications and evaluation of clinic blood pressure levels might be major limitations to this assumption, our data agree with other studies showing no independent impact of clinic blood pressure measurements on AoR size either in treated or untreated hypertensives.<sup>4-6</sup> Conversely, a recent report showed a direct significant association between nighttime blood pressure evaluated by ambulatory blood pressure monitoring and AoR diameter in hypertensive patients,<sup>7</sup> supporting the notion that pressure overload might indeed influence the AoR phenotype.

Although AoR dilatation may take place as a result of cardiac and hemodynamic factors, reverse causality may also occur. For instance, mild aortic regurgitation secondary to AoR dilatation could also influence cardiac output and cardiac remodeling.<sup>22</sup> In this context, our data from multivariate analysis showed that mild aortic regurgitation was indeed associated with AoR size/dilatation in both genders. Nevertheless, this variable did not explain the relationship between AoR dilatation and cardiac output in women and exerted no influence on the association between AoR dilatation and relative wall thickness in men, indicating that the cardiac and hemodynamic factors were related to AoR enlargement independently of aortic regurgitation. However, it must be acknowledged that the cross-sectional nature of our study does not exclude the possibility that the systemic hemodynamic parameters and LV remodeling were influenced by hemodynamic abnormalities secondary to the increased AoR size.

A notable result of our study was that men showed no variation in body size according to AoR diameter. This finding argues against data obtained from population-based and untreated hypertensives showing a direct impact of body surface area on AoR size.<sup>4-7</sup> Nonetheless, they seem to agree with the results obtained from patients with electrocardiographic LV hypertrophy, which showed no difference in the body surface areas of patients with either enlarged or normal AoR diameter.<sup>5</sup> It is noteworthy that most of the subjects with dilated AoR described in this aforementioned study were of male gender, thereby supporting the notion that body size may not be a major determinant of AoR dilatation in hypertensive hypertrophic men.

Left ventricular hypertrophy and carotid intima-media thickness have been independently related to microalbuminuria and retinal vascular changes in hypertensive subjects.<sup>26-28</sup> These observations raise the assumption that hypertension-induced cardiac and macrovascular damages share common pathophysiological mechanisms with microvascular disease. In this context, in this study, we evaluated whether there was a relationship between AoR size and markers of microvascular injury. Noticeably, we reproduced data from other

sources showing no association between AoR size and microalbuminuria.<sup>6,7</sup> Furthermore, we found that AoR size did not correlate with creatinine clearance and retinal vascular changes in both genders, thus suggesting that, in contrast to LV hypertrophy and carotid intima-media growth, AoR dilatation might not show an expressive relationship with hypertensive microvascular damage.

A potential limitation of this study is that the majority of hypertensive patients were on medications. Some findings might therefore be attributable to the differential effect of various therapy regimens. However, this hypothesis seems less probable as the univariate correlations showed no significant relationship between antihypertensive medications and AoR size in both genders. Moreover, we diminished this potential bias by considering the presence of antihypertensive treatment in multivariate models.

In conclusion, the present findings indicate that there are sex-specific determinants of AoR size in hypertensive patients with LV hypertrophy. In this regard, our results suggest that volume overload and central obesity are related to AoR dilatation in women, whereas AoR enlargement is associated more with LV myocardial growth and inflammatory status in men. Nevertheless, further longitudinal studies are required to confirm these assumptions.

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Supplementary Information accompanies the paper on Hypertension Research website (<http://www.nature.com/hr>)