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Clinical Research

Sex-Related Difference in Left Ventricular Mass in Nonhypertensive Young Adults: Role of Arterial Pressure

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ABSTRACT

Background: Blood pressure (BP) is higher in men than in women at similar ages through adult life. Interestingly, a similar pattern is detected in left ventricular mass (LVM), classically attributed to differences in body size. However, the existing difference in BP between sexes might be relevant in determining LVM and it has been not fully investigated. Therefore, we set out to determine the impact of nonhypertensive levels of BP on the sex-associated LVM difference.

Methods: We conducted population-based study including 283 young students (52% male; age 20.62 ± 1.31 years). BP was determined twice using standard mercury sphygmomanometers in 2 occasions. LVM was determined with M-mode echocardiography. To dissect the relative contribution of BP, volume load, and body size to the sex-related difference in LVM, an analysis of covariance was performed.

Results: Mean systolic and diastolic BP were 10.00 ± 0.96 and 4.59 ± 0.78 mm Hg higher and LVM was 34.87 ± 3.12 g larger in men than in women, respectively ($P < 0.01$, *t* test). When LVM was adjusted to mean BP, the sex difference was reduced by 16%. When LVM was adjusted to body size and hemodynamic load, this difference was reduced by 68.5%.

Conclusions: We report in a sample of young nonhypertensive students a difference in LVM between women and men that is partially explained (16%) by sex differences in BP, supporting an early effect of BP on cardiac mass even in the absence of hypertension. A more relevant effect could be expected as the population ages.

RÉSUMÉ

Introduction : La pression artérielle (PA) est plus élevée chez les hommes que chez les femmes à un âge similaire tout au long de leur vie adulte. Fait intéressant, un profil semblable est observé pour la masse ventriculaire gauche (MVG), traditionnellement attribuée aux différences de masse corporelle. Cependant, la différence de PA qui existe entre les sexes peut être pertinente pour établir la MVG, et cela n'a pas été complètement exploré. Par conséquent, nous comptons déterminer l'effet de la PA à des niveaux non hypertensifs sur la différence de MVG associée au sexe.

Méthodes : Nous avons mené une étude sur la population incluant 283 jeunes étudiants (52 % de sexe masculin; âgés de 20,62 ± 1,31 ans). La PA était prise deux fois en utilisant des sphygmomanomètres au mercure standards à 2 occasions. La MVG était définie par une échocardiographie en mode M. Pour examiner minutieusement la contribution relative de la PA, la charge volumique et la masse corporelle à la différence liée au sexe dans la MVG, une analyse de la covariance était faite.

Résultats : Les PA systolique et diastolique moyennes ont été plus élevées de 10,00 ± 0,96 et de 4,59 ± 0,78 mm Hg, et la MVG a été plus grande de 34,87 ± 3,12 g chez les hommes que chez les femmes, respectivement ($P < 0,01$, test t). Lorsque la MVG a été ajustée à la PA moyenne, la différence entre les sexes a été réduite de 16 %. Lorsque la MVG a été ajustée à la masse corporelle et à la charge hémodynamique, cette différence a été réduite de 68,5 %.

Conclusions : Nous rapportons dans un échantillon de jeunes étudiants non hypertendus une différence de la MVG entre les femmes et les hommes qui s'explique en partie (16 %) par les différences de la PA entre les sexes, soutenant un effet précoce de la PA sur la masse cardiaque, même en l'absence d'hypertension. On pourrait s'attendre à un effet plus pertinent à mesure que la population vieillit.

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII)[1] and the 2007 Guidelines for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)[2] represent the most recent references for blood pressure (BP) classification in adults. None of these guidelines consider differences in anthropometric characteristics or sex to categorize subjects according to their BP values. However, it is a well-established fact that BP is higher in men than in women at a similar age.[3,4] The difference in BP values between the sexes becomes detectable after childhood and persists through adult

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life; however, after menopause, BP increases in women as well.[4] Although the mechanisms responsible for this difference in BP are not clear, there is significant evidence, in both animal models and humans, that sex hormones play an important role.[5-10] Interestingly, a similar pattern in sex difference is detected in left ventricular mass (LVM).[11,12] This difference is small before the age of 12 years, whereas in all older-age strata LVM is 25%-38% greater in men than in women.[13] The entire variability of LVM between sexes is explained by body size in infancy; however, with increasing age, the ability of body size to precisely predict LVM decreases and the impact of hemodynamic load rises.[14] Even though a positive correlation between systolic BP (SBP) and LVM in young adults was clearly demonstrated in the **C**oronary **A**rtery **R**isk **D**evelopment **i**n Young **A**dults (CARDIA) study,[15,16] the relative contribution of the sex-associated difference in BP (considering only nonhypertensive individuals) on LVM variability has not been extensively analyzed in this age group.

This study attempts to examine the possibility that sex-related differences in BP detected after adolescence are responsible, at least in part, for the difference in LVM between nonhypertensive women and men.

Methods

Study population

The subjects of this study were medical students from the La Plata School of Medicine. All subjects (n = 283; 52% men) were between 19 and 24 years of age. Of the population screened, 29.7% were overweight and only 2.2% were obese. All subjects underwent echocardiography; however, 37 (25 men and 12 women) were excluded for being hypertensive (BP ≥ 140/90 mm Hg; n = 25) or obese (body mass index [BMI] ≥ 30; n = 10) or because there was inadequate echocardiogram quality to perform an accurate measurement (n = 2). Therefore, 246 subjects (123 men and 123 women) free of known cardiac disease were included in the analysis of LVM.

Family history of arterial hypertension (only in parents) and physical training were investigated. Those students who participated in aerobic physical activity (swimming, cycling, walking, and running) at least 45 minutes per day 3 times a week were considered "trained," while the remaining were classified as "nontrained."

The protocol adhered to the principles of the Declaration of Helsinki and was approved by the School of Medicine Review Board. All participants gave informed consent.

BP recordings

SBP and diastolic BP (DBP) were measured in the participants in the sitting position with the use of standard mercury sphygmomanometers and appropriate cuff sizes at least twice on 2 different occasions separated by a 1-week interval by especially trained technicians following JNC-VII recommendations.[1] The average of all measurements was considered to be the identity BP value of each individual. Mean arterial BP (MABP) was calculated as DBP + (SBP – DBP)/3, and pulse pressure (PP) as the difference between SBP and DBP.

Echocardiographic evaluation

Two-dimensional guided M-mode echocardiograms were performed with a 2- to 4-MHz phased array transducer (SonoSite Micro-Maxx; SonoSite Inc, Bothell, WA) with the subject in the partial left decubitus position after 20 minutes of rest. Echocardiographic recordings were read in a blinded manner by 2 investigators who had no knowledge of the subject's BP or other clinical data, and intraobserver and interobserver variability were assessed. Variability was expressed as a percentage by determining the absolute difference of measurements between readings and dividing by the measurement in initial reading. Intraobserver and interobserver variability were 5.1% and 10.9%, respectively, similar to or smaller than what has been reported.[16,17] LVM was determined following the American Society of Echocardiography recommendations: LVM (g) = $0.8\{1.04[(\text{LVIDd} + \text{PWTd} + \text{SWTd})^3 - (\text{LVIDd})^3]\} + 0.6$ g, where LVIDd is diastolic left ventricular (LV) internal diameter, PWTd is diastolic LV posterior wall thickness, and SWTd is diastolic septal thickness.[18] Stroke volume was estimated using the Teichholz correction of the cube formula.[19]

Anthropometric measurements

Body weight and height were measured with the subject wearing light clothing on the day of echocardiographic evaluation. To calculate the waist/hip ratio, waist circumference was measured in the supine position and hip circumference was measured in the standing position with use of an anthropometric tape. Body surface area (BSA) was estimated according to the DuBois and DuBois formula: $\text{BSA} = (\text{weight}^{0.425} \times \text{height}^{0.725}) \times 0.007184$, where the weight is given in kilograms and the height is given in centimetres. BMI was calculated as weight in kilograms/(height in metres)^2 as an index of obesity and height raised to 2.7 as a surrogate of fat-free body mass.[20] Obesity was identified by BMI ≥ 30 kg/m^2 and overweight by BMI > 25 kg/m^2 based on 1998 National Institutes of Health guidelines.[21]

Statistical analysis

Data expressed as mean ± SD was analyzed by SPSS 15.0 software (SPSS, Chicago, IL). Differences between 2 groups for continuous variables were assessed by *t* tests, with log transformation when needed to satisfy the assumption of normality. Linear regression analysis was performed between SBP and LVM.

The General Linear Model Univariate procedure was used to perform an analysis of covariance (ANCOVA) (SSPS 15.0) to estimate the difference in LVM between the sexes adjusted by different covariables (body size, SBP, and stroke volume). Since an extra assumption of the ANCOVA is that there is no significant interaction between the covariate and factor, a model with an interaction term to check homogeneity of the covariate coefficients was first performed. The significance values of the interaction terms were sex × PAS, $P = 0.615$; sex × PP, $P = 0.973$; sex × BSA, $P = 0.435$; sex × body height$^{2.7}$, $P = 0.167$; and sex × stroke volume, $P = 0.862$. Then, an ANCOVA was run to assess the effect of sex on LVM, after adjustment for the covariables. Values of $P < 0.05$ were considered statistically significant.

Table 1. General characteristics of the study sample

Parameter	Men (n = 148)	Women (n = 135)
Age, y	20.50 ± 1.27	20.75 ± 1.34
Height, m	1.75 ± 0.07	1.62 ± 0.06*
Weight, kg	72.46 ± 9.58	56.99 ± 0.63*
BSA, m^2	1.88 ± 0.14	1.60 ± 0.11*
BMI, kg/m^2	23.50 ± 2.49	21.83 ± 0.21*
SBP, mm Hg	124.30 ± 7.20	114.30 ± 7.80*
DBP, mm Hg	77.36 ± 6.59	72.77 ± 5.58*
PP, mm Hg	46.95 ± 6.47	41.53 ± 6.06*

Blood pressure values are the average of 4 determinations read on 2 different occasions. Values are expressed as mean ± SD. BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.

*Means $P < 0.05$, men vs women.

Results

The demographic characteristics and average SBP, DBP, MABP, and PP values in the population of women and men evaluated are outlined in Table 1. Hypertensive and obese subjects were excluded from this analysis since we were particularly interested in studying the putative effect of nonhypertensive BP values on LVM. As it can be appreciated, statistical significant differences in the anthropometric measurements such as BMI, BSA, height, and weight and in mean SBP, DBP, MABP, and PP values were observed between the sexes, with men's values being significantly greater than women's values in all cases.

The normal curves adjusted at the frequency distribution of SBP (Fig. 1, A) and DBP (Fig. 1, B) values in men and women are shown. Mean SBP, DBP, and PP values were 10.00 ± 0.96, 4.59 ± 0.78, and 5.42 ± 0.80 mm Hg higher in men than in women, respectively. Interestingly, our data also show a difference on BP values at the 95th percentile between the sexes (12 and 6 mm Hg higher in men than in women for SBP and DBP, respectively). LVM was estimated by echocardiography, and

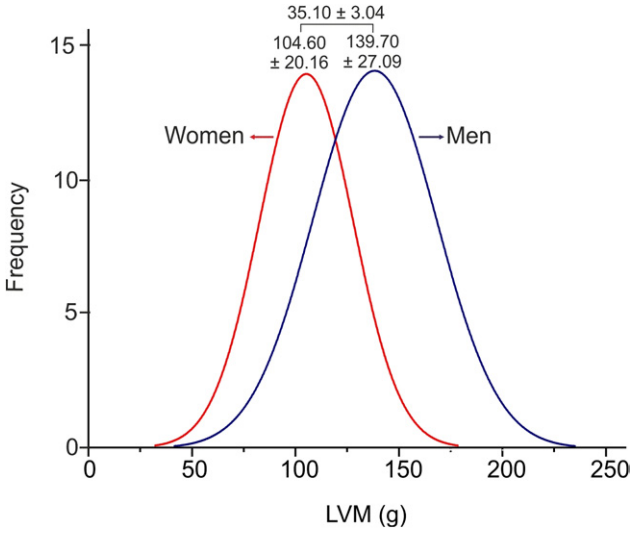

Figure 2. Normal curve fitted to the frequency distribution of left ventricular mass (LVM) (g) in women (**red**) and men (**blue**). LVM was on average 35 g larger in male than in female nonhypertensive young medical students.

a difference between the sexes of 35.10 ± 3.00 g, greater in men than in women ($P < 0.01$; t test), was observed (Fig. 2). When overweight students were excluded from this analysis, the sex-related difference in LVM was not significantly altered (32.02 ± 3.60, n = 199). As mentioned before, ≥ 2 other factors may be responsible for the sex-related difference in LVM: body size and hemodynamic load. When we analyzed the relationship between SBP and LVM in men and in women, 2 separate regression lines were observed, 1 for each sex (Fig. 3). For a given SBP, LVM was always greater in men than in women. Interestingly, both regression lines, although significantly separated at the "y-axis

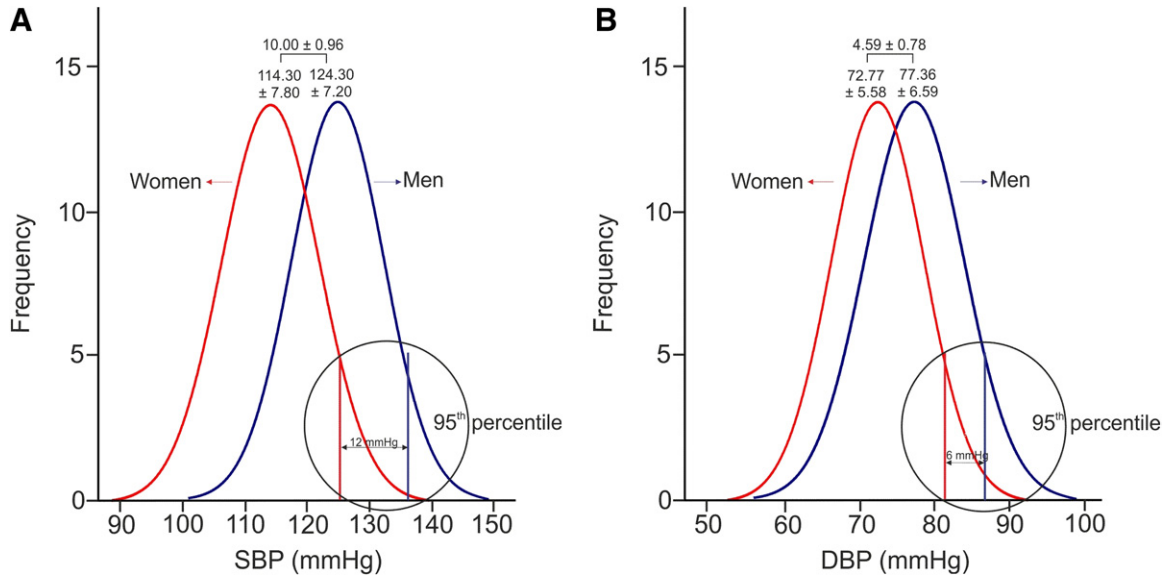

Figure 1. Normal curve fitted to the frequency distribution of systolic blood pressure (SBP) **(A)** and diastolic blood pressure (DBP) **(B)** values in each sex in the population of young medical students analyzed. Mean SBP and DBP were about 10 and 5 mm Hg higher in men (**blue**) than in women (**red**), respectively. These differences remain present at the 95th percentile as indicated with vertical lines.

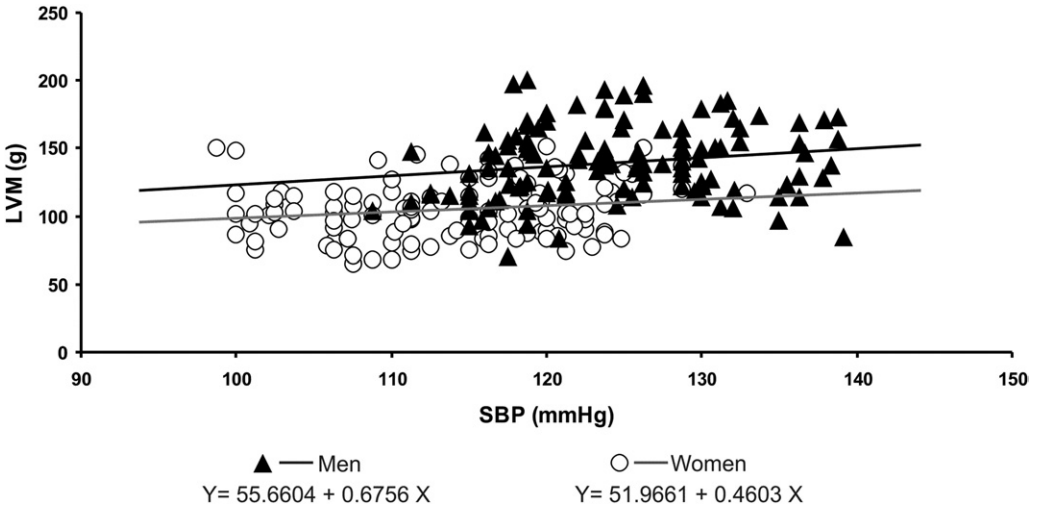

Figure 3. Linear regression analysis of the relationship between left ventricular mass (LVM) (g) and systolic blood pressure (SBP) (mm Hg) in men (**triangles, black line**) and women (**circles, gray line**). Two separate regression lines were observed, one for each sex that, although being significantly separated at the "*y*-axis interception," did not differ in the slope (0.6756 vs 0.4603, for men and women, respectively; nonsignificant). LVM was greater in men than in women at any SBP value, but the increment in LVM per 1–mm Hg of increase in SBP was not different between the sexes.

interception" (55.66 ± 41.98 g and 51.97 ± 26.38 g for men and women, respectively; $P < 0.001$), showed nonsignificantly different slopes (0.676 ± 0.337 g/mm Hg and 0.460 ± 0.230 g/mm Hg; $P = 0.59$). Therefore, a given increase in BP similarly increases LVM in both sexes, perpetuating the disparity in cardiac mass between women and men at different SBPs, making it necessary to look for other covariates to explain it.

Several different models of ANCOVA were run to estimate the sex-related difference in LVM using as covariates SBP, PP, BSA, body height$^{2.7}$, stroke volume, and the combination of the anthropometric variables with SBP and stroke volume. In all these models, sex, anthropometric variable, SBP, PP, and stroke volume significantly influenced LVM ($P < 0.05$). The results are depicted in Fig. 4. When LVM was adjusted to SBP, the sex-associated difference in LVM was reduced by 16%. The smallest residual difference in LVM between men and women was obtained after adjusting LVM to BSA, stroke volume, and SBP (11.06 ± 3.51 g; 95% confidence interval [CI], 17.96-4.16). Even though these adjustments markedly reduced the existing difference, they were not sufficient to completely abolish it.

In this age group, vigorous exercise and physical activity tend to be common and it is well known that regular training influences cardiac mass. Therefore, we compared LVM between regularly trained and nontrained students. No significant difference was detected between trained and nontrained women; however, a significant increase in LVM was observed in trained compared to nontrained men (Fig. 5, A). ANCOVAs were run to estimate the sex-related difference in LVM between nontrained and trained students at this time. When LVM was adjusted to SBP, the difference was reduced by 13% in nontrained and by 28% in trained students. Again, the smallest residual difference between the sexes was obtained after adjusting LVM to BSA, stroke volume, and SBP (9.36 ± 3.95; 95% CI, 17.16-1.56 g and 15.79 ± 7.33; and 95% CI, 30.43-1.15; g for nontrained and trained students, respectively [Fig. 5, B]).

Discussion

In this cross-sectional population-based study conducted in a large sample of young adults. we set out to ascertain the

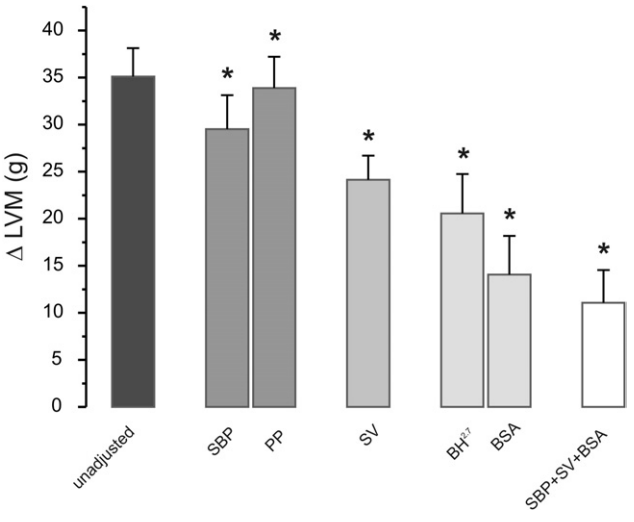

Figure 4. A sex-associated difference in between left ventricular mass (LVM) of 35.10 ± 3.00 g, greater in men than in women, was detected in the group of medical students in which an M-mode echocardiography was performed. The graph shows the results of the analysis of covariance that determined that the smallest residual difference in LVM between men and women was obtained adjusting LVM to body surface area (BSA), systolic blood pressure (SBP), and stroke volume (SV). Body height rise to 2.7 (BH$^{2.7}$) in metres. Pulse pressure (PP) in mm Hg. Similar results were obtained after also excluding from the analysis the overweight students. *Means $P <$ 0.01 vs unadjusted.

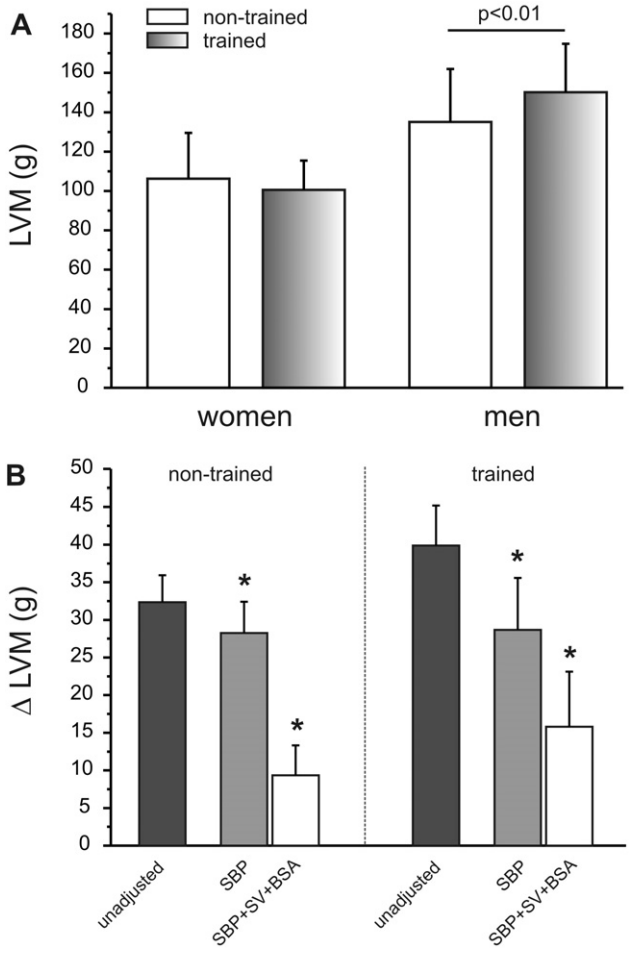

Figure 5. (A) The effect of regular physical activity on left ventricular mass (LVM) was evaluated in each sex. Nonsignificant difference was detected between trained and nontrained women; however, a significant increase in LVM was observed in trained compared to nontrained men. **(B)** The sex-associated difference in LVM was greater in the trained vs the nontrained students ($P < 0.01$, *t* test), probably reflecting difference in intensity and quality of physical activity between the sexes, too. When an analysis of covariance similar to that performed to the whole population of students was run for both groups separately, the smallest residual difference in LVM between male and female was obtained adjusting LVM to surface area (BSA), systolic blood pressure (SBP), and stroke volume (SV). *Means $P <$ 0.05 vs unadjusted.

impact of BP on determining the sex-associated difference in LVM. After excluding from the sample hypertensive and obese students, the sex-related difference in LVM was 35.10 ± 3.00 g greater in men than in women. The magnitude of the sex-related difference in LVM detected was significantly higher than that expected for the variability of the echocardiographic method used. The existence of a positive relationship between SBP and LVM in white or black young adults (23-40 years) of either sex has been previously demonstrated.[15,16] In our study, an ANCOVA determined that the higher BP values in men than in women accounted for about 6 g of the difference in LVM (approximately 16% of the total). At first glance, it may appear that the impact of BP on cardiac mass is, although statistically significant, small; however, we should keep in mind that these results were obtained in normotensive young adults. We do not know the impact of this difference in BP on these subjects as they age.

Even though current evidence supports that hemodynamic load (pressure and volume load) is the main stimulus leading to the development of left ventricular hypertrophy, BP under hypertensive values was not previously considered as a putative factor underlining the sex-associated difference in LVM that appears after puberty.[13] In the referred study, the authors excluded BP from the analysis based on the fact that all the subjects included in the study were nonhypertensive. Furthermore, since most of the sex-related difference in adult LVM was attributed to differences in body size, the presence of a "physiological" left ventricular hypertrophy was proposed. However, normotensive women and men have significantly different BP values as we demonstrated herein (Fig. 1) and as it was previously established by Muntner and colleagues[22] in different cohorts. Moreover, in a cohort of about 500,000 young Israelis, a difference in BP values similar to the one that we found was detected between boys and girls.[23] Interestingly, if we consider a statistic criterion (ie, the BP value at the 95th percentile) to separate subjects with normal BP from those with hypertension in this population of young medical students, the BP value for the cut-point would be different in each sex. At the 95th percentile SBP was about 12 mm Hg and DBP was about 6 mm Hg higher in men than in women ($P < 0.01$). Thus, in this age group, the statistic criterion would establish the cut-point between normotension and hypertension at 137/87 and 125/81 mm Hg for men and women, respectively. On contrary, if the same value for SBP and DBP is considered to define hypertension in both sexes, the prevalence will be greater in men. This premise is critical, since neither the JNC-VII nor the ESH-ESC considers different BP values to separately classify women and men. It is difficult to understand this discrepancy in the criteria proposed by the international guidelines to categorize subjects according to their BP values between the pediatric and the adult populations. For boys and girls younger than 18 years, different cut-points for each sex are used; however. this criterion is no longer applied once adulthood is reached.[1,24,25] This is especially important if we consider that the sex-related difference in LVM becomes detectable at puberty (between 12 and 14 years old) and persists during adulthood, similarly to what happens with BP.[13] The relationship between SBP and LVM found in our study supports an early effect of BP on cardiac mass even in the absence of hypertension.

The remaining difference in LVM detected between the sexes in our study after adjusting for SBP could be partially attributed to 3 other factors, namely body size, stroke volume, and unknown variables. With respect to the first 2 mentioned, lean body mass is the main determinant of the impact of both on LVM.[26,27] Therefore, normalization of LVM for body weight (that involves both lean and fat mass) does not represent the real impact of body size in overweight and obese people. A surrogate of lean body mass is body height, especially when obese people are excluded, as it was done in our study. Because height is a linear measure and mass is a 3-dimensional variable generated by a cubic function, the relation between them is linear only when height is raised to an exponent close to 3 (ie, 2.7).[28-30] When we used this last anthropometric measurement instead of the most widely accepted BSA to adjust for the sex-associated differences in LVM, the role played by body size and unknown factors changes to 41% and 43%, respectively.

In relation with the substantial proportion of the sex-related difference in LVM that could not be explained by recognizable factors (about 32 %), at least 3 possibilities should be discussed: genetic influences, sex hormones, and sympathetic tone.

1. *Genetic influences:* In studies of twins, it was shown that after adjusting for sex, arterial BP, and age, monozygotic twins have smaller within-pair differences in LVM than do dizygotic twins, suggesting that LVM was at least in part genetically determined.[31] Results from the **Hyper**tension **G**enetic **E**pidemiology **N**etwork (HyperGEN) study also supported that LVM is in part genetically determined.[32]

2. *Sex hormones:* Since LVM does not differ significantly between boys and girls until puberty, sex-specific hormonal influences appear to play a key role in determining the difference in LVM that increases during adolescence and remains during adulthood. The main hormonal factors to be considered are estrogens and testosterone. However, in this case we need to be cautious in differentiating between the direct effect these hormones have on LVM, independent of their well-known effect on body size and hemodynamic load. In connection with this, there is evidence supporting an inhibitory effect of estrogen in pathologic cardiac hypertrophy.[33,34] On the other hand, there is also significant evidence that androgens, such as testosterone, play an important role in sex-associated differences in BP regulation (for a review, see Reckelhoff [8]).

3. *Sympathetic tone:* A body of evidence indicates that sympathetic activation is significantly lower in females than in males.[35,36] An interesting study by O'Connell and colleagues[37] demonstrated a load-independent and sex-specific requirement for α_1-adrenergic receptors in the physiological hypertrophy of normal postnatal cardiac development. Recently, it was proposed that sympathetic nerve activity has a greater role in young men than in young women.[38]

In conclusion, we report in a sample of young nonhypertensive nonobese medical students a difference in LVM between women and men that can be partially explained (16%) by sex-related differences in arterial pressure. The relationship between SBP and LVM found in our study supports an early effect of BP on cardiac mass even in the absence of hypertension. Even though the impact of BP on cardiac mass may seem small, we should keep in mind that these results were obtained in normotensive young adults. We can speculate that a more relevant effect would be detected as the population ages.

Potential limitations of the study

Even though echocardiography is the most frequently used technique to measure cardiac mass, not only in epidemiologic and clinical studies but also in animal experimentation, it has limitations mainly derived by the intraobserver and interobserver variability. In the present study we used 2-dimensional guided M-mode, and this may have resulted in a greater variability.[17] However, and as it was stated previously, 2 investigators reviewed the images in a blinded manner to mitigate this limitation, and the variability measured in our examinations was smaller than the differences found in LVM between the sexes. On the other hand, the difficulty in obtaining good-quality images to perform the corresponding measurements was likely minimized by the population included in the study being nonobese and young.

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Disclosures

The authors have no potential conflicts of interest to disclose.

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