

Original Article

Sex-related differences in clinical, electrocardiographic, and echocardiographic indices among normotensive offspring of black parents with hypertension

ABSTRACT

Context: Blood pressure tracking has suggested that the difference in blood pressure between women and men begins to manifest during the adolescent period. It is therefore postulated that sex-related cardiac structural and functional differences that could predict future events may exist in the heart of offspring of parents with hypertension.

Aims: This study aimed at evaluating the effects of sex difference on the heart of offspring of parents with hypertension.

Settings and Design: Cross-sectional study.

Participants and Methods: A group of offspring of parents with hypertension aged between 15 and 25 years were recruited for the study if they had normal blood pressure and gave consent. They had clinical, electrocardiography, and echocardiographic assessments.

Results: Sixty-five participants consisting of 47 males and 18 females participated in the study. Mean systolic blood pressure was higher ($P=0.001$) in the males compared with the females but the diastolic blood pressure was similar between them. Electrocardiogram (ECG) parameters (heart rate, QRS axis and QTc) were similar between the males and the females but the summation of ECG voltage (SV2 + RV6) was higher in the former than the latter. Left ventricular (LV) posterior wall ($P=0.001$), aortic root diameter ($P=0.014$), LV mass ($P=0.001$), LV mass index ($P=0.001$), and relative wall thickness ($P=0.003$) were higher in the male compared with the female participants, respectively. However, more females (72.2%) had normal LV geometry compared with the males, $P=0.03$.

Conclusion: There are subtle clinical, electrocardiographic, and echocardiographic differences between the heart of male and female offspring of parents with hypertension with the former having more precursors of future cardiovascular events.

Keywords: Blood pressure, left ventricular mass, offspring, parents with hypertension, sex differences

INTRODUCTION

Cardiovascular disease is well documented to occur a decade earlier in men compared with women before the age of menopause.^[1,2] The difference in cardiovascular disease profile between the two sexes has been ascribed to difference in hormonal make-up. Estrogen hormone has cardioprotective effects and also acts as an immune-modulator of the inflammatory response in atherosclerosis.^[3] This has led to the exploration of the possible benefits of hormone replacement therapy in post-menopausal women to reduce the incidence of cardiovascular disease.^[4] However, some reports have demonstrated more left ventricular (LV) hypertrophy and

abnormal LV geometric pattern in women associated with adverse cardiovascular outcome than in men.^[5,6] The offspring of individuals with systemic hypertension are at an increased risk of developing hypertension and other cardiovascular disease later in life; and blood pressure

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tracking has suggested that the difference in blood pressure between women and men begins to manifest during the adolescent period.^[7] In addition, changes that occur during adolescent period may produce both hormonal and physical variations in boys and girls leading to difference in body weight and fat distribution. On the other hand, no significant difference has been observed in the systolic blood pressure (SBP) and diastolic blood pressure (DBP) of children <12 years of age.^[8] The final blood pressure of an individual is determined by both genetic and environmental factors.^[9] Strikingly, many studies have demonstrated higher SBP and DBP in men over all ages than in women.^[10-12] Similarly, on average men have higher body mass index (BMI) and larger waist circumference than women which may account for higher cardiovascular risk profile in the former than the latter. It is postulated that these sex-related differences in blood pressure and anthropometric characteristics could be present in the offspring of parents with hypertension and may influence early cardiac structural changes due to elevated blood pressure in these group of individuals, hence this study.

PARTICIPANTS AND METHODS

A cohort of patients with hypertension attending the cardiovascular clinic of hospital was randomly selected (using random numbers) after securing their consent to participate in the study. They were requested to make a list of their children's names and state their ages; and those who aged between 15 and 25 years were recruited for the study if they agreed to participate and had normal blood pressure. Ethical approval was obtained from the Ethics and Research Committee of the Hospital and informed consent was obtained from each participant.

Participants who were pregnant, had heart murmurs, structural heart disease, renal disease, on psychotropic drugs, or had cardiopulmonary disease were excluded from the study. All participants had a detailed clinical evaluation including the history of cardiovascular disease, anthropometric parameters, and blood pressure indices taken from each of them. Blood pressure was measured at the left arm in a comfortable position after about 10 min rest using an appropriate cuff. However, if the blood pressure was equal or >10 mmHg at the right arm, the latter blood pressure was used as the blood pressure of the participants. An average of three measurements was used as the blood pressure. Individuals with blood pressure $\geq 140/90$ mmHg or on antihypertensive drugs were also excluded. A 12-lead electrocardiogram (ECG) was acquired from each of the participants after they were well relaxed and the leads attached to appropriate positions in the

limbs and chest wall. A long parasternal 2D-guided M-mode echocardiogram was performed and measurement taken according to the recommendations of the American Society of Echocardiography.^[13] Parameters recorded included: LV internal dimension in diastole (LVIDd), LV internal dimension in systole (LVIDs), interventricular septal thickness in diastole (IVSd), interventricular septal thickness in systole, posterior wall thickness in diastole (PWd), posterior wall thickness in systole, LV ejection fraction (EF), and fractional shortening (FS). Others include right ventricular (RV) dimension in diastole, aortic dimension, and left atrial dimension. LV mass (LVM) was calculated using the formula:^[14] $0.8 \times \{1.04 \times [(LVIDd + IVSd + PWd)^3 - (LVIDd)^3]\} + 0.6$. LV mass index (LVMI) was determined using formula: LVM/BSA, where BSA is the body surface area. Relative wall thickness (RWT) was calculated by the formula: $2 \times PWd/LVIDd$. The pattern of LV remodeling was determined using LVMI and RWT. Increased RWT was present if RWT was ≥ 0.45 .^[15] LV geometric pattern was classified using RWT and LVMI as follows:

Normal geometry = normal LVMI and RWT;

Concentric remodeling = normal LVMI and RWT ≥ 0.45 ;

Eccentric LV hypertrophy = increased LVMI and RWT < 0.45 ;

Concentric LV hypertrophy = increased LVMI and RWT ≥ 0.45 .

Data analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 20.0 software (SPSS Inc., Chicago, IL, United States), and numerical values were presented as mean $\pm$ standard deviation. Student *t*-test was used to compare the means of continuous variables while chi-square test was used to compare the means of proportions. A statistically significant association was taken at $P < 0.05$.

RESULTS

Sixty-five participants consisting of 47 males and 18 females participated in the study. The mean age of the male participants was 22.0 (2.1) years which was similar to that of the female participants [20.8 (2.8), $P = 0.1$]. Comparison of other clinical and ECG parameters between the male and the female participants is shown in Table 1. Although the means of body weight and height of the male participants were higher ($P = 0.01$ and 0.001 , respectively) than that of the females, the mean BMI was similar between both sexes ($P = 0.53$). Similarly, the waist and hip circumferences were not different between the two groups of participants. The mean SBP was higher ($P = 0.001$) in the males compared with the females but the DBP was similar between the two sexes. All assessed ECG parameters

Table 1: Sex-differences in anthropometric, blood pressure, and ECG parameters among the participants

Parameter	Male (n = 47)	Female (n = 18)	P-value
	Mean (SD)	Mean (SD)	
Age (years)	22.0 (2.1)	20.8 (2.8)	0.10
Weight (kg)	66.5 (8.4)	59.3 (12.8)	0.01*
Height (m)	1.74 (0.07)	1.62 (0.06)	0.001*
BMI (kg/m ²)	21.96 (2.3)	22.5 (4.4)	0.53
WC (cm)	82.7 (9.6)	77.4 (7.1)	0.07
HC (cm)	90.4 (8.9)	88.4 (9.5)	0.51
SBP (mmHg)	120.1 (8.4)	113.3 (8.9)	0.01*
DBP (mmHg)	76.4 (6.9)	73.3 (9.1)	0.12
Heart rate (beats/min)	75.9 (10.9)	79.8 (11.6)	0.21
QRS axis (degree)	54.6 (27.2)	51.7 (20.7)	0.68
QTc (ms)	405.9 (32)	414.7 (38)	0.35
SV2 + RV6	37.2 (6.2)	24.0 (5.8)	0.001*

Key: ECG = electrocardiogram, SD = standard deviation, BMI = body mass index, WC = waist circumference, HC = hip circumference, SBP = systolic blood pressure, DBP = diastolic blood pressure, QTc = corrected QT interval. *Statistically significant.

(heart rate, QRS axis, and QTc) were similar between the males and the females but the summation of ECG voltage (SV2 + RV6) was higher in the male than the female participants.

Parameters of RV and LV dimensions are presented in Table 2. The RV internal dimension in diastole, the LVIDd and LVIDs, and the left atrial diastolic diameter were similar between the males and the females. On the other hand, LV posterior wall thickness ($P=0.001$) and aortic root diastolic diameter ($P=0.014$) were higher in the male compared with the female participants. Similarly, the LVM ($P=0.001$) and the LVMI ($P=0.001$) in the males were higher compared with that of the females. However, the LV EF and FS were similar between the male and the female participants.

LV geometric assessment is shown in Table 3. The prevalence of echocardiographic-assessed LV hypertrophy was 27.7% among the males compared with 16.7% in the females ($P=0.36$). RWT measured among the participants was higher in the males than in the females ($P=0.003$) and more females (72.2%) had normal LV geometry compared with the males, $P=0.03$. The prevalence of concentric remodeling, eccentric, and concentric left ventricular hypertrophy (LVH) was similar between both sexes.

Differences in the indices of LV diastolic function are displayed in Table 4. All parameters of diastolic function assessed among the participants were similar between the males and the females. However, deceleration time was significantly prolonged among the males compared with that of the females.

Table 2: Sex differences in parameters of cardiac dimensions and systolic function among the participants

Parameter	Male (n = 47)	Female (n = 18)	P-value
	Mean (SD)	Mean (SD)	
RVD (cm)	1.38 (0.48)	1.19 (0.32)	0.07
IVSD (cm)	1.13 (0.23)	1.08 (0.25)	0.49
PWD (cm)	1.04 (0.22)	0.79 (0.14)	0.001*
LVDD (cm)	4.67 (0.49)	4.28 (0.55)	0.53
LVSD (cm)	3.02 (0.71)	2.67 (0.38)	0.07
AOD (cm)	2.83 (0.27)	2.49 (0.16)	0.014*
LAD (cm)	3.01 (0.47)	3.08 (0.41)	0.81
LVM (g)	214.7 (61.2)	150.4 (45.0)	0.001*
LVMI (g/m ²)	123.7 (31.9)	90.7 (20.4)	0.001*
EF (%)	66.2 (9.2)	68.4 (5.7)	0.25
FS (%)	36.7 (7.4)	37.9 (4.3)	0.49

Key: SD = standard deviation, RVD = right ventricular dimension, IVSD = interventricular septal systolic dimension, PWD = posterior wall diastolic dimension, LVDD = left ventricular diastolic dimension, LVSD = left ventricular systolic dimension, AOD = aortic root diastolic dimension, LAD = left atrial diastolic dimension, LVM = left ventricular mass, LVMI = left ventricular mass index, EF = ejection fraction, FS = fractional shortening. *Statistically significant.

Table 3: Sex differences in prevalence of LVH and geometric patterns among the participants

Parameter	Male (n = 47)	Female (n = 18)	P-value
	Number (%)	Number (%)	
LVH	13 (27.7)	3 (16.7)	0.36
RWT	0.45 (0.12)	0.37 (0.08)	0.003*
Normal geometry	20 (42.6)	13 (72.2)	0.03*
Concentric remodeling	14 (29.8)	2 (11.1)	0.12
Eccentric LVH	6 (12.8)	2 (11.1)	0.53
Concentric LVH	7 (14.9)	1 (5.6)	0.3

LVH = left ventricular hypertrophy, RWT = relative wall thickness. *Statistically significant.

Table 4: Sex differences in indices of left ventricular diastolic function among the participants

Parameter	Male (n = 47)	Female (n = 18)	P-value
	Mean (SD)	Mean (SD)	
E (cm/s)	71.6 (11.25)	77.6 (15.0)	0.14
A (cm/s)	41.7 (9.1)	45.8 (11.1)	0.17
E/A ratio	1.80 (0.44)	1.73 (0.41)	0.54
IVRT (ms)	103.8 (9.5)	95.1 (19.7)	0.17
DT (ms)	258.3 (101.2)	182.4 (70.4)	0.002*
S (cm/s)	49.7 (10.2)	49.5 (8.5)	0.9
D (cm/s)	35.7 (17.6)	37.8 (10.9)	0.9
AR (cm/s)	25.7 (5.5)	25.2 (6.3)	0.9
Normal FP (NO%)	31 (66)	15 (83.3)	0.17
Restrictive FP (NO%)	16 (34)	3 (16.7)	0.17

Key: SD = standard deviation, E = mitral E velocity envelop, A = mitral A velocity envelop, IVRT = isovolumic relaxation time, DT = mitral E deceleration time, S = systolic velocity of pulmonary venous, D = diastolic velocity of pulmonary venous, AR = atrial reversal velocity of pulmonary venous. *Statistically significant.

DISCUSSION

Primary hypertension is a multifactorial and polygenic disease with incremental contributions from genetic and environmental determinants.^[16] This study explored the

role of sex on early changes that occur in the heart of offspring of parents with hypertension. The result showed that fewer number of females participated in the study which may be due to the fact that young females are often shy and may not be willing to be part of a study which could involve the exposure of their chest.

Assessment of anthropometric parameters showed that the males were taller and heavier compared with their female counterparts. This pattern has been well reported in literature indicating that the males on the average have higher body weight, height and BMI than the females during the adolescent and young adult period.^[17,18] Association between body weight and LV size has been reported previously and may contribute to early changes due to ventricular adaptation to hypertension. This reverses in many societies, because women often overtake men in terms of overweight and obesity toward middle age.^[19]

Blood pressure indices among the participants showed both the males and the females have normal SBP and DBP. However, mean SBP was higher among the male than the female participants. This concurs with the results of other studies which showed higher blood pressure values in the normotensive male than the female offspring of parents with hypertension.^[20,21] Differences in SBP may be a contributory factor to the differences observed in the heart of the male and female participants in this study.

Analysis of electrocardiographic parameters showed higher voltage generation among the male than the females participants. The males are generally more muscular compared with the females and this may influence their ECG voltage generation. The differences in ECG voltage at this stage could have implications for future cardiovascular events. Other ECG indices assessed were similar between the two groups.

Echocardiographic examination of the heart of participants showed higher posterior wall thickness, LVM, and LVMI among the males compared with the females. Higher mean SBP and the fact that the males are more muscular on average compared with the females may account for these differences between the two groups. Higher LV wall thickness and increased LVM had been shown to predict future cardiovascular complications in previous landmark studies.^[22,23] It is, therefore, not surprising that the males tend to have more cardiovascular disease and complications than the females because the precursors for future cardiac events are already present in disproportionate measure in the heart of the former than the latter during early stages of life.

Evaluation of LV geometry further refines cardiovascular risk assessment for future cardiac events. Although the pattern of abnormal LV geometry (concentric remodeling, eccentric LVH and concentric LVH) is similar between the males and the females, the latter had more normal geometry compared with the former. Similar RWT, a surrogate for abnormal geometry was higher among the males than the females. This further increases the risk of cardiac disease among the male than the female participants.

All parameters of diastolic function assessed were similar between the two groups except deceleration time of the mitral E velocity envelope. This also signifies early subtle difference between the heart of male and females participants.

These early echocardiographic differences between the hearts of males and females may have genetic basis such that genes that increase susceptibility to increase blood pressure may be co-inherited with those that determine LV thickness and mass.^[24] This is the basis of suggestion that systemic hypertension should be defined as a syndrome rather than by blood pressure numbers. Some of the early markers of systemic hypertension such as exaggerated blood pressure responses to exercise and diastolic dysfunction may be present before blood pressure elevation is sustained.

Estimates of heritability of blood pressures based on family studies are between 15 and 35%. In twin studies, heritability estimates for blood pressures are about 60% for males and between 30 and 40% for females.^[25] However, some studies have shown that the same candidate genes influence blood pressure in men and women. Genome-wide scan for blood pressure in Australian and Dutch participants suggest linkage at 5P, 14Q, and 17P for DBP and 13q34 for SBP.^[26] It has been suggested that many genes contribute to blood pressure variance and that each has only a small effect.

The first polymorphism to be implicated in LVH was the insertion/deletion polymorphism in intron16 of the angiotensin-converting enzyme gene in which DD genotype was identified as a potential genetic marker of LVH. The association of the DD genotype with LVH was stronger in men (odds ratio, 2.63; 95% confidence interval, 1.50–4.64; $P < 0.001$) than in women.^[27]

Similarly, in the Framingham Heart Study, heredity was found to contribute significantly to variability in LVM. Correlations between first-degree relatives were 0.15 (parent-child, $P < 0.001$) to 0.16 (siblings, $P < 0.001$), between second-degree

relatives the correlation was 0.06 ($P=NS$), and between spouses it was 0.05 ($P=NS$). The proportion of the variance in sex-specific LVM was 0.26 in men and 0.34 in women.^[28] In another study by Mayosi *et al.*, Sokolow-Lyon voltage linkage was on chromosome 10q23.1 [$\log_{10}$ of the odds (LOD=2.21; $P=0.0007$)], for ECG Cornell voltage product on chromosome 17p13.3 (LOD=2.67; $P=0.0002$), and for ECG LVM on chromosome 12q14.1 (LOD=2.19; $P=0.0007$), whereas echocardiographic LVM had possible linkage on chromosome 5p14.1 (LOD=1.6; $P=0.003$).^[29] Similar studies also identify candidate genes on chromosomes 3, 12, 19, and 15 to be linked with LVH.^[30] In addition, estrogen is also known to protect the cardiovascular system through the inhibition of signaling of aldosterone via mineralocorticoid receptor. This could explain why the female offspring had fewer abnormalities in their heart compared with the male counterparts.^[31]

In conclusion, there are subtle clinical, electrocardiographic, and echocardiographic differences in the heart of male and female offspring of parents with hypertension, with the former having more precursors of future cardiovascular events. There is the need for sex-specific preventive measures among the offspring of parents with hypertension and further studies to elucidate genetic factors that are involved in systemic hypertension.

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Conflicts of interest

There are no conflicts of interest.

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